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The Philippine Journal of Pathology (PJP) is an open-access, peer-reviewed, English language, medical science journal published by the Philippine Society of Pathologists, Inc. Committee on Publications. It shall serve as the official platform for publication of high quality original articles, case reports or series, feature articles, and editorials covering topics on clinical and anatomic pathology, laboratory medicine and medical technology, diagnostics, laboratory biosafety and biosecurity, as well as laboratory quality assurance. The journal's primary audience are Filipino laboratorians, diagnosticians, laboratory managers, pathologists, medical technologists, and all other medical and scientific disciplines interfacing with the laboratory. The PJP follows the **ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, EQUATOR Network Guidelines,** and **COPE Guidelines.** The PJP does not charge any article processing or submission fees from authors. It does not charge any subscription fees or download fees to access content.

On behalf of the *Philippine Society of Pathologists, Inc. (PSP)*, I extend my warmest congratulations to the editorial team of the *Philippine Journal of Pathology (PJP)* on the release of its first issue for 2025.

Since its revival in 2016, the PJP has steadily grown into a vital platform for Filipino pathologists and laboratorians—documenting our experiences, sharing new knowledge, and elevating the visibility of Philippine laboratory science. The Society is proud to have supported and sustained the operations of the journal through the years, recognizing it as a cornerstone of our academic and professional mission.

As the journal now takes steps toward international indexing, the need for robust, high-quality submissions becomes ever more urgent. I therefore call on all our members—consultants, residents, researchers, and educators—to support the PJP by submitting your manuscripts, whether original research, case reports, reviews, or viewpoints. Let us write about our unique cases, institutional experiences, innovations, and even the challenges we face. Each contribution, however modest, strengthens the journal and reinforces our collective voice.

The PJP is not just the official publication of our Society—it is a reflection of our commitment to excellence, scholarship, and the future of pathology in the Philippines. Let us continue to nurture and build it together.

Maria Cecilia F. Lim, MD, FPSP
President, Philippine Society of Pathologists, Inc.

Speech for the 75th Founding Anniversary of the Philippine Society of Pathologists with the Theme: Purpose and Solidarity

Aileen Riego-Javier, MD, FPSP

Esteemed colleagues, honored guests, and friends,

I have the extraordinary privilege to stand before you today as we gather to celebrate an extraordinary milestone—the 75th Founding Anniversary of the Philippine Society of Pathologists. Today, we commemorate a journey that has spanned seven decades—a journey defined by unwavering purpose, solidarity, and valuable contributions to the field of pathology and the broader medical community in our nation.

Seventy-five years ago, our predecessors laid the foundation for what we now proudly call our society, united by a shared mission: to enhance the standards of pathology, to elevate the health of our people, and to nurture the ideals of excellence, professionalism, and compassion. From the modest beginnings of a small group of dedicated individuals, the Philippine Society of Pathologists has grown into a vibrant community of experts, advocates, and pioneers, bound together by a collective purpose that transcends time and challenges.

May I just cite one aspect of the story of our Founding President, Dr. Liborio Gomez, who, despite the challenges of the early days of the Philippine Society of Pathologists, exemplified the purpose and solidarity that we celebrate today.

I quote, "Dr. Gomez was a strong and forceful influence upon thousands of young medical students, residents in Pathology and trained pathologists who came under his tutelage. He was the moving spirit in the organization of the Philippine Society of Pathologists and served as its first President. It is in his honor that the Dr. Liborio Gomez Memorial Award and Lecture was established.

An unfailing example of humility, dedication, and integrity, Dr. Gomez will always be remembered as a man whose visions had gone a long way in the realization of a dream. Dr. Liborio Gomez' story embodies the spirit of purpose and solidarity that continues to guide us today. It reminds us that even in the face of daunting challenges, our work has the power to transform lives and uplift our practice of Pathology."

Purpose is the heartbeat of our profession. It is the steady compass that guides our work, even in the face of uncertainty and adversity. In pathology, our purpose is clear: to seek truth through science, to diagnose with precision, to advocate for patient welfare, and to push the boundaries

of knowledge for the betterment of healthcare. We do this not for recognition or applause, but because we understand that in every specimen, in every microscopic slide, there is a life that depends on us. There is a family waiting for answers. There is a community yearning for hope.

Purpose/Mission of PSP

- To foster solidarity through proactive participation in society activities and advocacies enhanced communication and adherence to professional and ethical standards.
- To train highly competent pathologists by providing continuing education and training to our members.
- To lead the way towards the advancement in the field of Pathology and Laboratory Medicine through active participation in local and global collaborative research.
- To promote the role of socially responsible Pathologists in the healthcare system by coordinating with policy makers, stakeholders, other societies and healthcare partners in service, training and research in the local and international arena in support of the national health agenda.

Purpose/Vision of PSP

The Philippine Society of Pathologists will be a unified and cohesive force composed of highly competent, globally recognized professionals collaborating with local and international health partners, including the academe and other societies working towards the advancement of the profession of Pathology and Laboratory Medicine.

We will be at the forefront of patient care while adhering to the highest standards in service, training and research.

Yet, while purpose gives us direction, it is **solidarity** that can give us our collective strength. A shared commitment to collaboration, mentorship, and mutual support will enable us to overcome obstacles, to adapt to the ever-changing landscape of medicine, and to thrive in an environment that often demands more than we think we can give. In the past, we have weathered storms of crisis

after crisis, such as our organizational, national, and global crises. We have witnessed firsthand the need for solidarity. **Solidarity** is not merely the act of standing together; it is the spirit of lifting one another. Through **solidarity,** the coming together of minds, hearts, and hands, we amplify our impact. In our interconnected world, **collaboration** is not an option; it is a necessity. Together, we can meet the unprecedented challenges, proving that **unity** is not just a **value**, it is the greatest **asset** for organizations such as ours.

As we celebrate this momentous occasion, let us also reflect on the milestones that have shaped our journey:

1950: The Philippine Society of Pathologists (PSP) was founded, with its first organizational meeting held at the Aristocrat Restaurant on Roxas Boulevard, a far cry from what it is today.

1966: The Clinical Laboratory Law (RA 4688) was passed, defining the role of pathology in the country. In the same year, the PSP became an affiliate of the Philippine Medical Association. The Board of Pathology was also created.

1982: The PSP became incorporated.

1983: The PSP Ladies Circle and the Pathology Residents Organization were organized.

1984: Through the initiatives of Past Presidents Drs. Generoso Basa, Antonia Cruz-Basa, and Arsenio Cantos, a property was purchased for the future PSP building.

1986: Groundbreaking and cornerstone laying for the future PSP building. The PSP also became a member of the Asia Pacific Association of Societies of Pathologists.

1987: The maiden issue of the Philippine Journal of Pathology was published. The regional chapters were also established.

1991: The PSP, as a member of the Asia Pacific Association of Societies of Pathologists, hosted its convention in Manila, strengthening international collaboration.

2000: On its 50th Anniversary, the PSP celebrated with renewed commitment to excellence in health service, training, and research.

2015: Maria Ressa, 2021 Nobel Peace Prize laureate, was the Annual Convention speaker on "Truth in Diagnostics".

2019: PSP had an enhanced use of Information Technology (IT) with a dedicated website for the conventions and virtual slide case presentations in pathology, preempting the use of IT for the PSP's Continuing Education Program and other activities during the entire pandemic period.

These milestones are a testament to the enduring legacy of the Philippine Society of Pathologists and the collective efforts of its members to elevate the practice of pathology in the Philippines.

Today, as we celebrate the remarkable achievements of the past 75 years, let us also look to the future with renewed purpose and a deeper sense of solidarity.

"Character cannot be developed in ease and quiet. Only through experiences of trial and suffering can the soul be strengthened, vision cleared, ambition inspired, and success achieved." ***– Helen Keller***

PSP has the defining moment of equipping its members with strategies to use to spotlight the laboratory's pivotal role across not only clinical areas but also operations and case management.

Let us continue to inspire the next generation of pathologists, to embrace innovation and technology without losing sight of our humanity, and to champion equity in healthcare for all Filipinos.

Let us remain steadfast in our resolve to uphold the highest standards of our profession, not just for ourselves, but for the countless lives that are touched by our work.

Let us strengthen our ties with the broader medical community, with policymakers, and with the public, ensuring that pathology remains at the forefront of medical progress.

Above all, let us never lose sight of why we do what we do—for the betterment of lives, for the advancement of science, and for the brighter future that we build together.

In closing, as we commemorate 75 years of excellence, let us remember that this milestone is not just a celebration of our history, but a call to action for the years ahead. What does it mean to truly leave a legacy in the field of Pathology? May the spirit of purpose and solidarity inspire us to reach greater heights, to break new ground, to thrive, to lead, and to serve as a pillar of hope and excellence in our nation's healthcare system and to leave a legacy that future generations will be proud to inherit.

As we face an uncertain future, never in our history has there been a greater need for wise, courageous, and enlightened leadership than at the present. It is to you that we must look for that leadership.

Today, on our Diamond Anniversary, is an auspicious moment to mark that challenge. I challenge you to be heroes of our time. The world is waiting for that special contribution each one of you was born to make.

So, make a difference! We all have the extraordinary coded within us waiting to be released.

Release that energy, that extraordinary within- and follow your heart, your dream, your vision.

Thank you, and congratulations to all who have been part of this incredible journey. Together, let us continue to shape a future that reflects the very best of us, of who we are and what we stand for.

Mabuhay!!! Happy 75th Anniversary!!!

God bless the **Philippine Society of Pathologists!** ■

New Beginnings in a Lean Season

We open the first issue of the *Philippine Journal of Pathology* for 2025 with quiet resolve. It is, by all accounts, a lean harvest—just five articles in this issue—but each one reflects the rigor, relevance, and responsibility we seek to uphold in Philippine pathology. In an era marked by increasing demands on laboratory professionals and evolving health challenges, we recognize the many constraints faced by our contributors, reviewers, and editorial team alike. And yet, we publish—faithfully, persistently—because the work of knowledge-building must go on.

This year marks another step forward for the journal: we are introducing a new article type—**interviews with prominent pathologists and laboratorians**. These conversations offer first-hand perspectives on the most pressing issues in laboratory medicine in the country today, from workforce gaps and quality systems to research priorities and public health integration. It is our hope that these narratives will both inform and inspire, reminding us that behind every laboratory are individuals who carry the weight of expertise, decision-making, and institutional memory.

We also share that in 2025, PJP will begin the process of **applying for inclusion in international indexing platforms**. This is both a challenge and a commitment. We are under no illusions—our content, editorial processes, and publishing infrastructure will need to meet rigorous global standards. But we believe it is time. Filipino pathology deserves a seat at the global table, and the PJP will continue to grow as the platform through which our contributions are seen, cited, and shared.

We invite our readers, authors, and peer reviewers to join us in this endeavor. Submit your work. Cite local studies. Volunteer your expertise. Support your journal. In every published issue, no matter how modest in size, we are building a legacy of Philippine laboratory science—one article at a time.

Amado O. Tandoc III, MD, FPSP
Editor-in-Chief

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When Blood Becomes Life

Can you tell us a bit about yourself, your educational background, work experience, awards or other accomplishments, and other highlights of your career?

I am Ma. Lourdes U. Concepcion. A wife, mother of three, grandmother of one, a practicing Traditional Chinese Medicine (TCM) practitioner (Acupuncture, Qi gong), an Anatomic Pathology – Clinical Pathology (AP-CP) fellow. I taught Physiology for five years at the University of the East Ramon Magsaysay Memorial Medical Center (UERMMMC) and eight years in Pathology at the Ateneo de Manila University School of Medicine and Public Health (ASMPH); I retired from government service in 2023. I still work in a Local Government Unit (LGU) Health Department. As a Pathology resident (1992-1995), I was assigned to Mobile Blood Donations in 1994. This was when Philippine Children's Medical Center (PCMC) was slowly transitioning from buying blood from commercial blood banks to collecting blood from voluntary blood donors. Since then, I have been involved with the Blood Bank, ultimately becoming the Pediatric Blood Center chair in 2015 until 2023. In between these years, I served at the PSP's Board of Governors (BOG) and Board of Pathology (BOP). The Philippine Blood Coordinating Council (PBCC) was the venue for me to train other medically allied professionals in blood banking. The DOH also sent me to various workshops, local and abroad, all for the improvement of blood transfusion services in the country. I was also with the Philippine Blood Center on several capacities since its inception. The PCMC Pediatric Blood Center (PedBC) has received awards: the Civil Commission's Gawad Pag-asa Awards in 2001; Sandugo Awards from 2001-2005 by the DOH; Second runner-up in the International Society for Blood Transfusion (ISBT) award for developing countries in 2018, Canada. And I have been awarded the Philippine Blood Coordinating Council Jorge M. Peralta Lecture Award, 2018 and the Bronze Medal for Excellence for Health Services during Crisis at the World Hospital Congress, Dubai 2022. I view all these awards as recognition of the collective efforts of colleagues and staff. They were a proof of the PCMC Blood Bank's commitment to uphold the standards of VBD and transfusion practices in the Quezon City area, particularly in the field of pediatrics. The highlights of my career? To witness the residents and interns I have trained excel in this field and embrace the call for a safe, quality, affordable and accessible blood/blood products.

I am honored to be assigned Chair of the National Council for Blood Services (NCBS) technical committee to help formulate standards and guidelines for the operation of the blood services and to ensure the highest levels of quality and safety for donors, patients and staff.

What is your take on the current blood safety and blood supply landscape in the Philippines?

There is a dire need for a stronger political will to prioritize the blood services program of the country, then the blood supply will be safe, will be of quality, accessible, and affordable. We are often described as the calamity capital of the world, after all.

What would you consider as weaknesses or challenges in the blood program?

The blood program is not a standalone program of DOH. As part of the Public Health Services Cluster (PHSC), its partners or networks are with Centers for Health Development (CHDs), LGUs, Non-Government Organizations (NGOs), Civil Society and People's Organization, and other government agencies at regional/provincial/city/municipal level and the private sector. If all these partners have the same standards to follow and carry out the mandates they were given in the interest of safety to all, then the program will be valuable and meaningful. Harmonization of the regulations and standards that are comprehensible to all stakeholders still needs to be implemented. This is a basic need that requires urgent attention and collaboration.

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The Philippine Children's Medical Center (PCMC) Pediatric Blood Center (PedBC).

Second runner-up in the International Society for Blood Transfusion (ISBT) award for developing countries in 2018, Canada.

The Bronze Medal for Excellence for Health Services during Crisis at the World Hospital Congress, Dubai 2022.

The Philippine Blood Coordinating Council (PBCC) Jorge M. Peralta Lecture Award, 2018.

*I am honored to be assigned **Chair of the National Council for Blood Services (NCBS) technical committee** to help formulate standards and guidelines for the operation of the blood services and to ensure the highest levels of quality and safety for donors, patients and staff.*

What key reforms do you think should be undertaken to advance the blood program in the country?

A clear direction from the NCBS Executive committee as regards standards with close collaboration with the regulatory agency. A panel of experts in government is essential to guide and monitor all processes applied to the blood unit from the donor to the recipient. Regular and open communication among the blood services, not only to share blood units, but also to share best practices and help the blood service facilities thrive in a limited resource country like ours. The increased use of social media and technology can raise awareness on the need for blood from volunteers.

How optimistic are you that we will be able to achieve stronger blood supply systems?

I am hopeful that each step, no matter how small, will improve the lives of the patients we serve. It was 30 years ago, when I witnessed the slow but sure phase out of the high-risk commercial blood banks. I was then part of the system when buying blood from commercial blood banks was the standard. I hope for a future where safe blood is universally accessible to patients across the Philippines.

OPEN ACCESS – ORIGINAL ARTICLE

Value of Cell Block Technique as an Adjunct to Smear Cytology in Thyroid Fine-Needle Aspiration Biopsy

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ABSTRACT

Background. Thyroid fine-needle aspiration biopsy (FNAB) is widely used for thyroid nodule characterization, with approximately 2.7% of samples classified as "inadequate." Non-diagnostic samples pose limitations, resulting in repeated procedures, and unnecessary diagnostic thyroidectomies. Conventional smear (CS) is commonly the method of choice for cytologic preparation of thyroid FNAB. The cell block technique is an alternative that concentrates cells providing additional material for better evaluation and ancillary testing. While conventional smears are commonly used, introducing routine complementary cell blocks could potentially lower costs associated with repeat procedures and improve patient management.

Objective. The study aimed to investigate the diagnostic value of incorporating the cell block technique as adjunct to conventional smear technique in reducing nondiagnostic rates (Bethesda Category I) in thyroid-fine needle aspiration biopsies (FNAB) conducted in two private hospitals.

Methodology. This is a multi-center, retrospective cross-sectional study with 701 samples from 528 adult patients, who underwent thyroid FNAB between January 2020 – September 2022. The primary outcome of interest is the reduction in non-diagnostic rates with the combined use of conventional smears and cell block.

Results. The non-diagnostic rates were significantly higher with cell block technique (28.10%) as compared to conventional smears (16.26%), *p*-value <0.01. The results show that conventional smears have lower non-diagnostic rates. With smear cytology alone, 114 (16.3%) of all samples were nondiagnostic. With the addition of cell block technique, 15 of these samples were reclassified as benign (n = 13), Bethesda III (n = 1) or Bethesda IV (n = 1). The rest of the non-diagnostic samples (n = 99) remained Bethesda I. Overall, the equivalent decrease in non-diagnostic rate was 2.1%

Conclusion. The combined use of cell block and conventional smears did not significantly decrease nondiagnostic rates in thyroid FNAB. In general, conventional smears demonstrated superior diagnostic efficacy across all Bethesda categories, establishing it as the preferred sampling preparation method for thyroid FNAB. Cell blocks should be considered a supplementary technique, particularly in cases where ancillary methods like immunohistochemistry or molecular testing are needed.

Key words: fine needle biopsy, thyroid nodule, Bethesda I, thyroid gland, thyroid diseases, thyroid nodules, non-diagnostic smears, cell block, Bethesda System, thyroid cytopathology

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INTRODUCTION

Thyroid nodules are a common clinical problem, and fine-needle aspiration biopsy (FNAB) under ultrasonographic guidance is a valuable diagnostic tool for characterizing thyroid nodules. This procedure is safe, minimally invasive, has high patient tolerability and is the most accurate and cost-effective method for selecting patients for surgery.[1]

Thyroid FNA biopsy has a positive predictive value of >97% for malignant cytology, and is the procedure of choice for evaluation of thyroid nodules.[2,3] The Bethesda system for Reporting Thyroid Cytopathology (TBSRTC) is used for standardized classification of thyroid fine needle aspiration specimens. According to this system, each report is placed under 6 possible categories: (I) nondiagnostic; (II) benign; (III) atypia of undetermined significance (AUS); (IV) follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant.

Non-diagnostic/inadequate cytology is one of the most important limitations of thyroid FNAB. Non-diagnostic samples still carry a 5-20% risk of malignancy.[4] Non-diagnostic specimens (Bethesda Classification I) occur when the samples contain only cyst fluid, lacks cellular material, or contains confounding factors such as: obscuring blood, clotting/drying artifacts or specimens contaminated by gel/diluted by blood or fluid. Repeat ultrasound-guided FNAB and monitoring is recommended in these patients. This leads to repeat biopsies, increased patient anxiety, and unnecessary diagnostic thyroidectomies with its associated additional costs.

Conventional smear (CS) has traditionally been the method of choice in the cytologic preparation of thyroid FNA biopsies. Some drawbacks with this technique include presence of artifacts, variable cellularity, cellular breakdown, and limited sample preservation. The conventional smear can be used alongside other alternative and more recently introduced techniques such as cell blocks (CB) and liquid-based cytology (LBC) to improve diagnostic rates.

The cell block technique is a histological preparation method used to create a solid, tissue-like specimen from aspirated materials. It allows for better evaluation of architectural patterns and cell structures, which can be especially helpful in cases where a definitive diagnosis is challenging based on conventional cytological evaluation alone. In cases where the FNAB sample is limited or contains scant cellular material, the cell block technique can concentrate the cells, making it possible to create a more informative specimen for analysis. In cytologically indeterminate nodules, it also allows for ancillary studies such as immunohistochemistry (IHC) or molecular testing, which can provide further insights into the characteristics of the nodules. Immunohistochemical stains can help diagnose uncommon thyroid neoplasms, as well as those with uncertain histogenesis. Testing for HBME-1, GAL-3, and CK19 immunopositivity has a high sensitivity and specificity for the diagnosis of papillary thyroid cancer.[5]

Molecular testing for BRAF V600E mutation helps characterize nodules that are positive for papillary thyroid cancer.[6]

Previous reports have indicated that the use of cell blocks in combination with conventional smears have resulted in enhanced diagnostic yield and accuracy for various type of specimens.[7,8] However, there is conflicting data about the utility of the addition of cell block in FNA biopsies of thyroid nodules.

A retrospective study of 11,011 thyroid nodules from 10,206 patients examined the utility of combined cell block with conventional smears in improving diagnostic accuracy in thyroid FNAB. When CS and CB were performed in combination, the unsatisfactory rate decreased to 9.8% versus 18.1% found in samples processed with CS alone (p <0.001). This study found that the combined utilization of CS and CB can substantially reduce the unsatisfactory rate of thyroid fine needle aspirations and enhance diagnostic effectiveness. Therefore, CB should be regularly employed in the evaluation of thyroid nodules whenever possible.[9]

In another study of 328 consecutive patients who underwent ultrasound-guided thyroid FNAB, samples were processed using both CS and CB technique. Rapid on-site evaluation of all specimens was performed to evaluate adequacy. In this study, comparing the nondiagnostic/unsatisfactory rates, it was observed that the addition of the cell block to the conventional smears significantly reduced the rate of nondiagnostic samples (17.1% vs. 4.3%, P <0.001). The overall accuracy of CS with CB for detection of neoplasm was 94%, with a sensitivity and specificity of 100% and 90%, respectively. By utilizing a combination of techniques such as CS and CB, the representativeness of samples has been enhanced, leading to reduced false negative rates. This combined approach can be routinely employed in thyroid FNAB.[10]

Conversely, a small retrospective study evaluated 82 thyroid FNAB cases that underwent review of both conventional smears and cell blocks. The examination of cell block slides revealed a non-diagnostic rate of 10% (8 out of 82 cases). This study found that cell blocks did not offer significant assistance in majority of cases. They proved contributory in only 31% (25 of 82 cases), and of the neoplastic cases only 22% (5 out of 23 cases) of cell blocks contributed to the diagnosis. The minimal contribution of cell blocks in diagnosing thyroid lesions was due to the low cellularity observed.[11]

Findings from another retrospective study examining 150 cell blocks generated from 252 thyroid FNAB cases, reviewed alongside their original smears, revealed a non-diagnostic rate of 18.5%. Within this study, cell block interpretation did not demonstrate any additional benefit over cytology slides in 63% (95 out of 150) of all thyroid FNAB cases. The agreement between CS and CB interpretations based on the TBSRTC classification was observed in only 35% of cases. The generation of cell blocks provided additional diagnostic value in only 2% (3 out of 150) of FNAB samples, and this improvement was attributed to the application of immunohistochemistry in samples suspected to be of medullary thyroid carcinoma (MTC). In conclusion, this study highlights that routine processing of cell blocks in thyroid FNAB did not significantly enhance the diagnostic yield of unsatisfactory or atypical thyroid samples. Routine processing of cell blocks is time-consuming, impractical, and introduces delays in the turnaround time of results. The authors suggest generating cell blocks only in cases classified as TBSRTC Category IV and V when immunohistochemistry stains are necessary for diagnostic purposes.[12]

Despite conflicting evidence, optimized techniques in thyroid FNAB have some advantages and may have utility in our setting. In the Philippines, most samples are processed by conventional smears alone. Non-diagnostic/inadequate smears necessitate additional healthcare costs, associated with prolonged diagnostic investigations and unnecessary follow-up visits. The cell block technique may minimize the need for repeat biopsies, potentially reducing overall costs and improve patient management. However, the cost-effectiveness of this technique depends largely on the local healthcare system, the availability of resources, and the expertise of the medical staff. Further research and consideration of local factors are necessary to determine

the feasibility and appropriateness of adopting cell block technique routinely in such settings.

OBJECTIVES

This study aimed to investigate the diagnostic value of incorporating the cell block technique as an adjunct to conventional smear technique in reducing non-diagnostic rates (Bethesda Category I) in thyroid fine-needle aspiration biopsies (FNAB) conducted at a private hospital. Specifically, it sought to determine the demographic profile and pathological findings of participants; evaluate and compare the non-diagnostic rates of conventional smears and the cell block technique; analyze the distribution of benign, malignant, and other pathological findings from both methods; assess the reduction in non-diagnostic yield when using the combined approach; and compare the concordance of pathological findings between the two techniques.

METHODOLOGY

Study design and population

This is a retrospective, cross-sectional study comparing the non-diagnostic yield rates (Bethesda Category I) and other pathologic findings of combined conventional smears and cell block technique with conventional smears alone in FNA biopsies of thyroid nodules at St Luke's Medical Center Quezon City and Providence Hospital from January 2020 to September 2022. Adults 18 years of age and older, who underwent FNAB of the thyroid were included in the study. The relevant clinical data of the included participants were obtained from electronic medical health records. Patients who underwent fine needle aspiration biopsy of organs other than the thyroid (lymph nodes/parathyroid/salivary glands), biopsy done in patients post thyroidectomy and/or post radioactive iodine ablation, patients with incomplete data in the medical records, and those patients who underwent other procedures such as thyroid cyst aspiration/ethanol ablation of thyroid nodules were excluded.

Description of outcome measures

The primary outcome of this study is to determine the non-diagnostic/unsatisfactory rate (Bethesda Classification I). This will be expressed as a dichotomous variable.

"Others": those specimens with a cytologic diagnosis of either:

b.1 Benign
b.2 Atypia of undetermined significance (AUS)
b.3 Follicular neoplasm
b.4 Suspicious for malignancy
b.5 Malignant

c. Concordance rate: the rate of agreement of histologic diagnosis (as expressed by the Bethesda classification/Bethesda system for reporting thyroid cytopathology) between samples prepared by conventional smear vs cell-block technique

Study procedures and data gathering

Potential study participants who underwent thyroid fine needle aspiration biopsy were screened from the logbook and other registries of the Diabetes and Endocrine centers of St. Luke's Medical Center, Quezon City and Providence Hospital. The participants demographic, clinical characteristics, ultrasonography, histopathology, and cytopathology results were obtained from electronic medical health records.

All biopsies were performed under ultrasonographic guidance. Biopsies were performed by endocrinologists, surgeons (from ENT and General Surgery) and pathologists at the Endocrine centers of both institutions.

In cases where mixed solid and cystic nodules were present, samples were taken from the solid components. On each pass, the first half of the sample was extruded onto the glass slides for preparation of conventional smears, while the remaining material was submitted for cell block technique. The same technique was repeated on any subsequent passes. Samples were prepared using both conventional smears and cell block technique. For conventional smears, the extracted material was expelled onto a glass slide, gently spread, and then immediately fixed by immersing in 95% ethanol for fixation. For the cell block technique, needle rinses were done into a clean container with 30 mL of 10% buffered formalin solution from the material left in the hub of the needle. The packed sediment/fibrin clot was prepared by centrifugation of the test tube at 2000 revolutions per minute (RPM) for ten minutes. The sediment/fibrin clot was processed for histopathology. The clotted material was transferred into filter paper, folded and shifted into carefully labelled cassettes. The tissue cassettes were then added into a jar of formalin for fixation. The residual drops of specimen at the bottom of the previously centrifuged test tube were then gently spread on glass slides, fixed in 95% ethyl alcohol and prepared for Papanicolaou staining. Each specimen was labelled from either right, isthmus, or left nodule accordingly.

Samples were submitted to the pathology department labelled with the patient's name, age, sex, hospital pin number as well as biopsy site. For patients with samples obtained from nodules on multiple sites, samples from each site (left lobe, right lobe or isthmus) were included and analyzed as distinct data. When multiple nodules were present on one site/lobe, the first nodule biopsied with samples submitted for both conventional smear and cell block technique were chosen. No rapid on-site assessment was conducted to determine the adequacy of the specimens.

All conventional smears and cell blocks were evaluated and classified by pathologists of their respective institutions. The histopathologic diagnoses were categorized according to The Bethesda System for Reporting Thyroid Cytopathology specimens.

Sample size

Using a 5% significance level, a 5% margin of error, and 12.8% change in Bethesda I (non-diagnostic) classification as reported by de Cristo et al. (2016)[10], the required sample size was computed at 172 biopsies.

Statistical analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the patients. Frequency and proportion were used for categorical variables such as sex,

nodule laterality, and Bethesda classification, median and range for non-normally distributed interval/ratio variables such as age.

For categorical variables, Fisher's Exact test was used to determine the difference in frequencies between groups (Conventional Smear (CS) vs Cell block technique (CB)). Cohen's Kappa was used to determine the concordance rate or the agreement of nominal/ordinal variables such as the Bethesda classification of the Conventional Smear and Cell block. Missing variables were neither replaced nor estimated. The null hypothesis was rejected at a significance level of 0.05α.R-4.1.3 was used for data analysis.

Ethical considerations

The Clinical Protocol and all relevant documents were reviewed and approved by the SLMC Institutional Ethics Review Committee. Patient confidentiality was respected by ensuring anonymity of patient records. Each patient document was CODED and did not contain any identifying information to ensure confidentiality. All study data were recorded, and investigators were responsible for the integrity of the data i.e. accuracy, completeness, legibility, originality, timeliness and consistency. The study abided by the Principles of Declaration of Helsinki and was conducted along the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP). The authors declare that there was no conflict of interest with study collaborators, and subjects.

RESULTS

This study presents the clinicodemographic profile of 528 patients who underwent fine-needle aspiration biopsy of thyroid nodules (Table 1). The median age of the patients was 51.50 years, ranging from 18 to 85 years. In terms of sex distribution, females predominated the study, comprising 86.17% (455 out of 528) of the participants, while males constituted a smaller fraction of 13.83% (73 out of 528).

When considering the laterality of the nodules, right-sided nodules were slightly more common, with a frequency of 51.50% (361 out of 528), while left-sided nodules accounted for 44.51% (312 out of 528) of the cases. Isthmic nodules, found in the narrow part of the thyroid gland connecting the two lobes, were relatively rare, representing only 3.99% (28 out of 528) of the patients.

The cross-tabulation table (Table 2) provides a comparative overview of the Bethesda classifications for conventional smears and cell block techniques. It highlights the distribution of results across the different Bethesda categories, offering an insight into the concordance and discordance of diagnoses made by these two methods.

We observed a high concordance rate for category II (Benign), with 355 out of 434 cases (81.56%) being classified as benign by both techniques. However, there is a notable discordance in Category I (Nondiagnostic), where the cell block technique resulted in a much higher frequency (28.10%) compared to conventional smears (16.26%).

In Table 3, the concordance rate of Bethesda classification between conventional smears and cell block technique was evaluated using Cohen's Kappa, a statistical measure of agreement. The study included a total of 701 cases.

The overall Kappa value obtained for all Bethesda classifications combined was 0.679, indicating a substantial level of agreement between conventional smear and cell block technique interpretations. This suggests that there is consistency between the two methods in classifying cases into different Bethesda categories.

The study results revealed individual Kappa values for each Bethesda classification, ranging from 0.533 to 0.892. These values indicate varying degrees of agreement between conventional smear and cell block technique for specific categories. The Kappa values of 0.533, 0.677, and 0.749, corresponding to Bethesda I (Nondiagnostic), Bethesda II (Benign), and Bethesda III (Atypical cells of undetermined significance - AUS), respectively, demonstrate moderate to substantial agreement.

For the categories Bethesda IV (Follicular CA/ Suspicious for follicular CA), Bethesda V (Suspicious for malignancy), and Bethesda VI (Malignant), the Kappa values of 0.894, 0.865, and 0.892, respectively, indicate near-perfect agreement between the two methods. All the Kappa values had p-values less than 0.01, confirming that the observed agreements between conventional smear and cell block technique classifications are statistically significant.

Table 4 provides a comparison of the results obtained using conventional smears and cell block techniques for the assessment of thyroid nodules. The results are classified according to the Bethesda System for Reporting Thyroid Cytopathology, and a total of 701 samples were analyzed for each technique.

Table 1. Clinicodemographic profile of patients who underwent thyroid fine needle aspiration

	Median (Range); Frequency (%)
Age, years	51.50 (18 - 85)
Sex	
Male	73 (13.83)
Female	455 (86.17)
Nodule laterality	
Left	312 (44.51)
Right	361 (51.50)
Isthmus	28 (3.99)

Table 2. Cross tabulation of the Bethesda classification of conventional smear and cell block technique (n = 701)

		Cell Block						
		I	II	III	IV	V	VI	Total
Conventional Smear	*I*	99 (14.1)	13 (1.9)	1 (0.1)	1 (0.1)	0	0	114 (16.26)
	II	78 (11.1)	355 (50.6)	1 (0.1)	0	0	0	434 (61.91)
	III	16 (2.3)	12 (1.7)	55 (7.8)	0	0	0	83 (11.84)
	IV	1 (0.1)	1 (0.1)	0	13 (1.9)	0	0	15 (2.14)
	V	2 (0.3)	3 (0.4)	2 (0.3)	0	27 (3.9)	0	34 (4.85)
	VI	1 (0.1)	2 (0.3)	0	0	1 (0.1)	17 (2.4)	21 (3.00)
	Total	197 (28.1)	386 (55.06)	59 (8.42)	14 (2.00)	28 (3.99)	17 (2.43)	701 (100)

Table values are in frequency (%).

Table 3. Concordance rate of Bethesda classification of conventional smear vs cell block technique (n = 701)

	Kappa	Interpretation	*p*
Overall	.679	Substantial	<.01
Bethesda I – Nondiagnostic	.533	Moderate	<.01
Bethesda II – Benign	.677	Substantial	<.01
Bethesda III – AUS	.749	Substantial	<.01
Bethesda IV – Follicular CA	.894	Near Perfect	<.01
Bethesda V – Suspicious for malignancy	.865	Near Perfect	<.01
Bethesda VI – Malignant	.892	Near Perfect	<.01

Statistical analysis used: Cohen's Kappa.
Kappa interpretation; 0, no agreement; 0.1-0.2, slight agreement; 0.21-0.4, fair agreement; 0.41-0.6, moderate agreement; 0.61-0.8, substantial agreement; 0.81-0.9, near perfect agreement; 1, perfect agreement.

Table 4. Differences in Bethesda classification using smear alone and combined smear-cell block interpretation (n = 701)

Bethesda category	Smear	Smear + Cell block	No change	Stepped up	Stepped down	Total
	Frequency (%)					
I	114 (16.26)	99 (14.12)	99 (14.12)	15 (2.14)	0	114 (16.26)
II	434 (61.91)	433 (61.77)	355 (50.64)	1 (0.14)	78 (11.13)	434 (61.91)
III	83 (11.84)	83 (11.84)	55 (7.85)	0	28 (3.99)	83 (11.84)
IV	15 (2.14)	15 (2.14)	13 (1.85)	0	2 (0.29)	15 (2.14)
V	34 (4.85)	34 (4.85)	27 (3.85)	0	7 (1.00)	34 (4.85)
VI	21 (3.00)	21 (3.00)	17 (2.43)	0	4 (0.57)	21 (3.00)
Total	701 (100)	685 (97.72)	566 (80.74)	16 (2.28)	119 (16.98)	701 (100)

The non-diagnostic rates were significantly higher with cell block technique (28.10%) as compared to conventional smears (16.26%). Conventional smears alone yielded a higher percentage of benign results (61.91%) than cell block technique (55.06%). For category III (Atypia of Undetermined Significance, AUS), conventional smears reported a higher percentage (11.84%) compared to cell block technique (8.42%). Furthermore, very slight differences were observed in the categories IV (Follicular Neoplasm/ Suspicious for a Follicular Neoplasm), V (Suspicious for Malignancy), and VI (Malignant) between the two techniques, with conventional smear generally reporting slightly higher percentages.

The results show that conventional smears have lower non-diagnostic rates when compared to cell block technique. While differences were observed in the categories suggestive of or confirming malignancy, these differences were minimal. With smear cytology alone, 114 (16.3%) of all samples were non-diagnostic. With the addition of cell block technique, 15 of these samples were reclassified as benign (n=13), Bethesda III (n=1) or Bethesda IV (n=1). The rest of the non-diagnostic samples (n=99) remained Bethesda I. Overall, the equivalent decrease in non-diagnostic rate was 2.1% (Table 4).

Conventional smears tagged 434 (61.9%) of biopsies as benign, but the addition of cell block recategorized only 1 sample to Bethesda III (AUS). In contrast, adding cell block technique to conventional smear cytology did not increase the risk category of any of the samples initially graded as Bethesda III - VI. Hence, overall, cell block technique as an adjunct to conventional smear resulted in a higher risk category for only 3 in 701 samples (0.4%), or 3 in 528 patients (0.6%).

DISCUSSION

Fine-needle aspiration biopsy plays a crucial role in the initial screening of suspicious thyroid nodules. It has demonstrated reproducibility, high diagnostic accuracy, and has also resulted in improved patient selection for conservative management or surgical treatment. Despite its clinical significance, FNAB has certain limitations, such as inadequate sampling and limited cellularity of obtained samples.

The cell block technique has been routinely employed as a technique for evaluating tissue from fine-needle aspirations or fluid aspirations. While the smear technique has been universally used for detection of malignancy in thyroid FNAB, the use of cell blocks has been adopted to enhance diagnostic accuracy. Cell blocks offer diagnostic architectural information that complements fine-needle aspiration smears and allows for the application of ancillary tests such as immunohistochemistry and molecular testing on the preserved cellular material. This can provide additional diagnostic information and aids in characterizing certain thyroid nodules. This can lead to definitive diagnoses, providing crucial information for developing targeted treatment strategies.

It has been established that the diagnostic accuracy of FNAB is significantly improved when performed under ultrasonographic guidance, alongside an accompanying onsite cytopathologist.[13,14] Similarly, lower FNAB sampling inadequacy is associated with operator experience.[15] Non-diagnostic rates are lower in specialty groups with high procedural volumes (>600 within a group practice/year) than those with low volumes (<105/year).[16] All thyroid FNA biopsies in this study were done with ultrasound guidance, but without the presence of an onsite cytopathologist to

assess for sample adequacy. Also, thyroid FNA biopsies in this study were done by various specialists with differing levels of experience. Specimens were collected from specialists from Endocrinology, General surgery, Ear, Nose and Throat (ENT), as well as Pathology.

The results of this study offer a detailed comparison of the conventional smear and cell block technique using the Bethesda System for Reporting Thyroid Cytopathology. The key finding is the high level of concordance between the two methods across most Bethesda categories, as indicated by substantial to near-perfect Kappa values. This high concordance, particularly in categories IV, V, and VI, which indicate potential malignancy, suggests a robust reliability of both techniques in detecting malignant or suspicious thyroid nodules. Clinicians can thus have confidence in the diagnostic consistency of these two methods.

However, a notable discordance was observed in the Bethesda I (non-diagnostic) category, with higher frequency of non-diagnostic samples in the cell block technique compared to conventional smears. The addition of cell block to conventional smears meanwhile, yielded a non-significant decrease in the non-diagnostic rates. This suggests that the routine addition of cell blocks to conventional smears in thyroid FNAB does not improve diagnostic accuracy.

Given these findings, the routine addition of cell block to conventional smears for thyroid nodule evaluation should also consider other factors such as turnaround time, cost, and local expertise. The turnaround times for histopathologic diagnosis for thyroid FNAB samples with conventional cytology smears and cell blocks of 2321 specimens from 1826 patients were evaluated. Of the 2321 samples, 933 had cell block smears prepared. The study found that cases with cell blocks had longer turnaround times compared to those without. Cases with cell blocks were more likely to have a turnaround time more than 1 day (65%, $P < 0.0001$) or greater than 3 days (25.4%, $P < 0.0001$). This led to a longer workaround time, increasing patient's waiting time and increased hospital billing costs. The longer turnaround time, increased utilization of resources and workforce allocation could be potentially reduced if cell blocks were produced only as needed, particularly when smear results are inconclusive or if ancillary tests are necessary to confirm the diagnosis.[17]

Sample processing via the cell block technique require technical skills. This entails specialized machinery and staff who are trained to handle, process and interpret the cell block smears for an accurate histologic diagnosis. Currently, cell blocks are not consistently valuable in improving diagnostic rates, with insufficient sample cellularity being the primary factor.

The greater proportion of inadequate samples with the cell block technique compared to conventional smears in this study, could also be attributed to the sampling method or improper triage of the sample. At our institutions, cell block material is currently obtained through a needle rinse after each pass. To enhance the diagnostic yield of cell block preparations, an alternative approach is to perform a dedicated needle pass with the specific purpose to obtain cell block material. This method offers a higher probability of obtaining an adequately cellular specimen, compared to relying solely on a needle rinse at the end of each pass.[18]

Ensuring careful and strategic allocation of samples among smears and cell blocks is also important.[19] Lastly, close collaboration between the pathologists and interventionalists to develop effective specimen processing protocols may lead to better diagnostic outcomes. These practices may increase the probability of obtaining sufficient samples for histologic diagnosis, ancillary testing and help avoid the need for repeated procedures.

Limitations

This study has several limitations. First, data was collected by retrospective chart review, and a secondary examination of each conventional smear and cell block slide to determine their contributory status to histopathologic diagnosis could not done. In this study, FNA biopsies were conducted by various interventionalists, each having different levels of expertise and procedural volume. Likewise, the evaluation of the conventional and cell block smears for each participant was performed by different cytopathologists, and the readers were unblinded.

Lastly, there was no correlation of thyroid FNA biopsy results with histology. To further determine diagnostic accuracy, a comparison of both conventional smear and cell block with the gold standard of post-surgical histopathology is ideal. Such a comparison would provide a more comprehensive and accurate evaluation of their diagnostic accuracy.

CONCLUSION

The routine addition of cell block to conventional smears did not significantly decrease non-diagnostic rates in thyroid FNA biopsies. In general, conventional smears demonstrated superior diagnostic efficacy, establishing it as the preferred sampling preparation method for thyroid FNAB. Cell block should be considered as a supplementary technique in establishing the diagnosis in equivocal cases, and when ancillary methods like immunohistochemistry or molecular testing are required. The authors recommend that cell block be used as a supplementary technique in establishing the diagnosis specifically in equivocal cases, particularly when ancillary methods such as immunohistochemistry or molecular testing are required.

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ANNEX

Operational Definitions

Fine needle aspiration biopsy of the thyroid: diagnostic tool which is a simple procedure that involves passing a thin needle through the skin to sample fluid or tissue from a cyst or solid mass in the thyroid

Conventional smear: technique in the preparation of samples of thyroid fine-needle aspiration biopsies which is done by gently expelling extracted material from the syringe onto a glass slide, gently spreading, and then immediately fixed by immersing in 95% ethanol for fixation

Cell-block technique: a technique in the preparation of samples of thyroid fine-needle aspiration biopsies which is done by injecting the extracted material from the syringe into a container with 30 mL of 10% buffered formalin solution or 95% ethanol, then subjected to cytospin (centrifuged for 10 min. at 2000 rpm), then stained with hematoxylin and eosin (H&E).

Bethesda classification/Bethesda system for reporting thyroid cytopathology: a standardized, category-based reporting system for thyroid fine-needle aspiration biopsy (FNAB) specimens. It is composed of 6 categories, namely:

Nondiagnostic or unsatisfactory: specimen containing cyst fluid only, virtually acellular specimen, or other (with obscuring blood or clotting artifact)

Benign: specimen consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.), consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context, consistent with granulomatous (subacute) thyroiditis

Atypia of undetermined significance (AUS): specimen that contains few cells that have distinct but mild nuclear atypia or with more extensive but very mild nuclear atypia

Follicular neoplasm: specimens with most of the follicular cells arranged in cell crowding or microfollicle formation

Suspicious for malignancy: specimen suspicious of papillary thyroid carcinoma, suspicious for medullary carcinoma, suspicious for metastatic carcinoma, suspicious for lymphoma

Malignant: specimen showing features of Papillary thyroid carcinoma, Poorly differentiated carcinoma, Medullary thyroid carcinoma, Undifferentiated (anaplastic) carcinoma, Squamous-cell carcinoma, Carcinoma with mixed features, Metastatic carcinoma, Non-Hodgkin lymphoma, or others

OPEN ACCESS – ORIGINAL ARTICLE

Upgrade Rate and Associated Predictive Factors of Papillary Breast Lesions on Core Needle Biopsy in a Private Tertiary Institution: A Cross-sectional Study

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ABSTRACT

Objective. The aim of this study was to determine the upgrade rate in diagnosis of biopsy-proven papillary breast lesions on core needle biopsy and their respective surgical excisions, and to assess for predictive factors associated with an upgrade at St. Luke's Medical Center – Global City.

Methodology. A retrospective review of our institution's database identified 184 papillary breast lesions diagnosed by core needle biopsy. The study population consisted of 71 samples that met the inclusion criteria. The overall upgrade and concordance rates were determined and analyzed if there was any significant association with clinical demographics, radiologic findings, and core diameter on gross examination. Continuous variables were presented as mean and median, and Shapiro-Wilk test was used to assess normality of data. Categorical variables were expressed as frequencies and percentages. Simple logistic regression analysis with Firth's bias correction was performed to determine the variables associated with a diagnostic upgrade. *P* values ≤0.05 were considered statistically significant.

Results. A total 71 patients, all female, were included in the study. The overall upgrade rate was 8.45% (95% CI: 3.16-17.49%) in comparison with the diagnosis of the initial CNB and SE alone. This translated to 6/71 samples in this study. The overall concordance was 91.55% based on clinical significance, and an individual diagnosis concordance rate of 78.87%. None of the predictive factors (i.e., age, history of breast cancer, BI-RADS score, and gross core diameter) assessed showed an association with a diagnostic upgrade.

Conclusion. The computed overall upgrade rate is within range of currently published literature. The concordance rates for both clinical significance and individual diagnosis were quite high, suggesting good reproducibility of histopathologic diagnosis within our institution. This was also found to be consistent with other studies. Of the predictive factors, none showed an association to a diagnostic upgrade. Despite the latter, our findings may be of value within the medical center in further exploring and expanding the data set at hand, such that it may hopefully contribute to local guidelines in managing PBLs in the future.

Key words: papilloma, papillary breast lesions, upgrade rate, core needle biopsy

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INTRODUCTION

Papillary breast lesions (PBL) are a diverse and heterogeneous group of breast lesions that include benign intraductal papillomas (IDP), papillomas with atypical ductal hyperplasia (ADH, atypia measuring <3 mm), papillomas with ductal carcinoma in situ (DCIS; atypia >3 mm), papillary DCIS, encapsulated papillary carcinomas (EPC), solid papillary carcinomas (SPC), and invasive papillary carcinomas (IPC).[1-3] A conundrum frequently faced by surgical pathologists is that papillary morphology alone – epithelial cells lining arborizing, delicate fibrovascular cores, with or without a myoepithelial cell (MEC) layer and are attached to the ductal walls – is challenging in the face of core biopsies, where commonly, only portions of the papillary lesion are sampled and submitted for analysis. The characteristics of the epithelial cells, as well as the presence of the MEC layer, determine whether a papillary lesion is categorized as benign or atypical.[1-4] In many cases, immunohistochemical stains are utilized to further determine characteristics where morphology is difficult in determining the lesion's nature.[1,2,5-7]

Determination of the upgrade rate, and factors associated with the upgrade rate of papillary lesions on core biopsy to atypical or outright malignant in resection, can be useful in the management of papillary breast lesions – especially in those that could potentially benefit the patient if a more severe underlying lesion cannot be totally ruled out. The data gathered can serve as a guide to both the pathologist and surgeon, for the next best course of action if a patient should undergo surgical excision (SE) of the lesion or not, and thus the possibility of avoiding an unnecessary procedure.[4]

A common dilemma encountered by pathologists after a diagnosis of an atypical papillary lesion made on core needle biopsy (CNB) is whether to recommend conservative management or excision of the lesion.[8,9] A core biopsy only provides a representative picture of the lesion found in radiographic studies. Nonetheless, an overly aggressive management of the patient may occur depending on the diagnosis reported by the pathologist.

Immunohistochemical techniques that detect the MEC layer or epithelium have been of great utility in identifying and differentiating benign versus atypical lesions.[1,5-7] However, other factors such as age (demographic), lesion size, and radiologic findings have been also found to correlate with the upgrade to an atypical papillary lesion.[1,4,5,8-11] At present, there has been no uniform consensus as to the criteria that should be employed in the management of patients with papillary breast lesions.[12] This is exhibited by European guidelines preferring a more conservative approach through regular patient follow-up,[13] while guidelines proposed by the American Society of Breast Surgeons suggest surgical excision is more appropriate.[14]

Papillary breast lesions evaluated on core needle biopsy is not an uncommon task in the realm of surgical pathology. As part of cancer screening programs, Image Guided CNB (IGCNB) has become more utilized, and becoming the "gold standard" in diagnosing breast masses and lesions and in further evaluating their malignant potential.[1,15,16] Particularly difficult are PBLs, due to their wide range of disease potentials from benign to frank malignancy.[1-5,8-12,15-17]

Another layer adding to the difficulty in diagnosing papillary lesions is sampling, wherein the architecture of the lesion may be distorted due to fragmentation, infarction, or inadequacy of the specimen. Further, the presence of cellular atypia cannot be entirely ruled out since a biopsy takes only a snapshot of the lesion identified through imaging.[3,13,18] In Europe,[13] the uncertainty this raises has led to the consensus that PBLs are lesions of uncertain malignant potential, or B3 on a biopsy category scale of 5 (B1 to B5), regardless of cellular atypia identified in the sample. All these factors are taken into consideration when evaluating for the upgrade rate i.e., the percentage of benign neoplasm that becomes classified as atypical papillary neoplasm or frank malignancy. Qiu et al., suggests that the upgrade rate for PBLs may vary up to 31%.[5]

This variance in upgrade rate has therefore led to some controversy as to which factors associated with the upgrade of the lesion can be used in the subsequent clinical and surgical management of PBLs. Various publications have identified common factors including: older age (ranging from 45 to 65 years),[1,9,19] larger lesion size (between 1 to ≥2 cm)[1,19-21] and presence of atypia.[5,6,13,19,2-28] Other factors such as location (central or peripheral), radiologic grade (Breast Imaging Reporting and Data System - BI-RADS score), microcalcifications, and history of breast cancer had less than conclusive results.[1,10,22,24,29,30] The inconsistencies in these findings may be attributed, but not limited to sample size and interobserver variability as well as other confounding variables.

To note, interobserver variability has been reduced due to in no small part by the utilization of immunohistochemical (IHC) studies.[5] Myoepithelial markers (i.e. p63, SMMS) and epithelial markers (i.e. ER, CK5/6) have aided in reducing the ambiguity in the diagnosis of lesions that by morphology alone are difficult to discern for atypia.[1,3,10] Despite this, it should be reiterated that the presence of atypia regardless of using IHC stains, can still be confounded if the IGCNB sampling of the lesion was unable to hit the area containing the atypical cells in the first place, hence the need for criteria in whether clinical observation or surgical excision should be the next step in the management of the patient's case. Establishing an upgrade rate within our tertiary medical center with a breast care center should be of benefit within the institution for clinicians and pathologists alike.

The study primarily aims to determine the upgrade rate of papillary breast lesions on core needle biopsy and its subsequent surgical excision (SE) specimens. Moreover, the association between clinico-demographic (age), history of breast cancer, gross core diameter, radiographic findings and the various papillary breast lesions will be examined.

METHODOLOGY

This is a single center, analytical, cross-sectional study approved by the Institutional Ethics Review Committee (IERC) of St. Luke's Medical Center – Global City (SLMC-GC), which abided by the Principles of the Declaration of Helsinki (2013) and conducted along the Guidelines of the International Conference on Harmonization - Good Clinical Practice (ICH-GCP) on privacy and confidentiality.

Patient selection

A retrospective review of breast core needle biopsies with papillary lesions from the time period of January 1, 2020 to December 31, 2023, were sourced from the records of the Section of Histopathology of SLMC-GC, where an initial total of 184 records were found. Those included into the study were the surgical pathology reports of CNBs with an initial diagnosis of a PBL, age as demographic data, core diameter from the gross description, history of breast cancer, an available BI-RADS score from the Breast Care Center via breast ultrasonography or mammogram, and the CNB must have a subsequent SE specimen. Those excluded were as follows: 1) an initial biopsy done through incision or excision biopsy; 2) excision and resection specimens who had no initial CNB; 3) incomplete demographic data; and 4) those without radiographic data (BI-RADS score) done within the medical center.

Data analysis

Data collection was done via utilization of the laboratory information system (LIS) and electronic medical records (EMR). The following keywords were used to search through both databases: "breast," "papilloma," and "papillary." Radiologic data (BI-RADS score) was accomplished through assistance of the records kept within the Breast Care Center of SLMC-GC.

Data gathered included an initial core biopsy of a PBL, its respective subsequent surgical excision, patient characteristics (age at the time of biopsy, history of breast cancer), core diameter from the gross description of the surgical pathology report, and BI-RADS score. MS Excel was used to input the data.

Patient characteristics were analyzed as follows: age was categorized as <55 years old, and ≥55 years old; and history of breast cancer as "yes" or "no." Radiologic data of the BI-RADS score was group together into three categories: "1,2,3;" "4," and "5,6." Core gauge was set as a continuous variable.

The PBLs were classified as benign, atypical, or malignant. Intraductal papilloma was categorized as benign. For atypical lesions, inclusive was papilloma with atypical ductal hyperplasia. Within the malignant category, the following were included: papillomas with DCIS, papillary DCIS, encapsulated papillary carcinomas, solid papillary carcinomas, and invasive breast carcinomas (IBC) with papillary features/ invasive papillary carcinomas.

For the purposes of this study, surgical pathology reports that stated "*ductal carcinoma in situ in papillary pattern*" were included, as it is common to have multiple DCIS morphological patterns in one specimen.[31] In addition, "*invasive breast carcinoma with papillary features*" are also included in the study, as invasive papillary carcinoma in its pure form is rare.[2]

Upgrade rate is defined as the percentage in which a benign neoplasm is upgraded to an atypical papillary neoplasm, and by which an atypical papillary neoplasm is upgraded into a frank malignancy. Concordance is the percentage at which the initial diagnosis of the core needle biopsy matches that of the SE specimen.

Data was encoded in MS Excel by the researcher. Stata MP version 17 software was used for data processing and analysis. Continuous variables (i.e., age and diameter of needle) were presented as mean (standard deviation/SD) and median (interquartile range/IQR) depending on the data distribution. The Shapiro-Wilk test was used to assess the normality of data. Categorical variables (i.e., history of breast cancer, BI-RADS score and histopathologic results) were expressed as frequencies and percentages. To determine the variables associated with upgrade of lesions, simple logistic regression analysis with Firth's bias correction was performed. P values ≤0.05 were considered statistically significant.

RESULTS

A total of 184 patients with core needle biopsies showing PBLs were identified between January 2020 to December 2023. Seventy-one (39%) of the 184 patients were recorded as having underwent a subsequent SE and met the inclusion criteria and thus included into the study. The characteristics of the patients (age, history of breast cancer), BI-RADS score, and core diameter are noted in Table 1. All the samples in this study were taken from female patients.

Patient characteristics

The mean age was found to be 58.2 ± 14.1 years old, with a range of 24 to 90 years old. Forty-five (63%) of the samples were from patients with an age of ≥55 years, with the remaining 26 (37%) below 55 years of age. Of the 71 samples, only 1 (1%) patient had a previous history of breast cancer prior to CNB. For BI-RADS score, 32 (45%) samples were found to be category 4, followed by category 5, 6 with 28 (39%) samples, and BI-RADS category 1, 2, and 3 with 11 (16%) samples. The median core diameter was found to be 0.2 cm in 44 (62%) of the samples.

Distribution of papillary breast lesions

Figure 1 illustrates that based on the CNB (1.a) and subsequent SE (1.b) results of the included patients, most were noted to have been diagnosed with invasive breast carcinoma with papillary features / invasive papillary carcinoma. None were found to have a papilloma with DCIS.

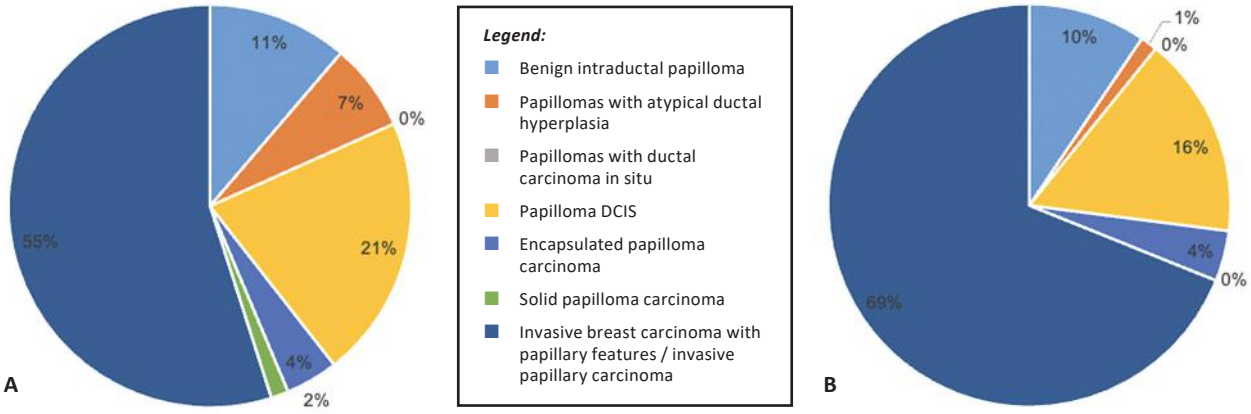

Figure 1. Distribution of papillary lesions based on **(A)** CNB results and **(B)** histopathology result of resection specimen (n = 71).

Concordance rate and upgrade rate

Table 3 shows the concordance of the CNB and their subsequent SE results based on specific diagnosis. Pertinent findings include that one patient had SPC on CNB, which was then found to have been DCIS with papillary features / papillary DCIS upon SE. Further, all IBC with papillary features / invasive papillary carcinoma diagnosed on CNB retained the diagnosis on SE.

Table 3 further classifies concordance based on clinical significance, namely, benign, atypical, or malignant. Noteworthy was that all (100%) four atypical lesions on CNB were upgraded to a malignancy. Also, all 58 malignant PBLs on CNB remained malignant upon SE.

After data analysis, the results of the overall upgrade and concordance rates are summarized in Table 4.

Predictive factors

A simple logistic regression model was used in determining the significance of the predictive factors and their potential association with an upgrade in diagnosis.

Table 1. Characteristics of patients with papillary lesions on CNB and underwent resection (N = 71)

Characteristics	n (%) Mean ± SD; Median [IQR]
Age (in years), mean	58.2 ± 14.1
<55	26 (37)
≥55	45 (63)
History of breast cancer, % yes	1 (1)
BI-RADS score	
1, 2, 3	11 (16)
4	32 (45)
5, 6	28 (39)
Core diameter (in cm), median	0.2 [IQR: 0.2-0.2]

The analysis of age-related findings revealed that among individuals younger than 55 years, 8% (2 out of 26 samples) experienced an upgrade in diagnosis, while the remaining 92% (24 samples) did not. Similarly, for those aged 55 and older, 9% (4 out of 45 samples) saw an upgrade in diagnosis, with 91% (41 samples) showing no change.

The findings regarding breast cancer history indicated that 9% (6 out of 70 samples) with no history of breast cancer experienced an upgrade in the diagnosis of their PBL, while 91% (64 samples) did not. Among those with a history of breast cancer, none (0 out of 1) had an upgrade in diagnosis.

Analysis of BI-RADS score groups revealed that for BI-RADS 1, 2, and 3, none of the samples (0%, 11 out of 11) showed an upgrade in diagnosis. In the BI-RADS 4 category, 19% (6 out of 32 samples) experienced an upgrade, while 81% (26 samples) did not. Similarly, all samples in the BI-RADS 5 and 6 groups (100%, 28 out of 28) showed no diagnostic upgrade.

Across all samples, regardless of whether an upgrade in diagnosis occurred, the median core diameter was consistently 0.2 cm, with an interquartile range (IQR) of 0.2 to 0.2.

The simple logistics regression model analysis revealed that none of the factors were significantly associated with an upgrade in diagnosis of PBLs (Table 5); thus, a multiple logistic regression model was no longer created.

DISCUSSION

The diversity of PBLs account for 1 to 4% of breast lesions diagnosed though CNB.[23] Patients with benign IDPs have a

Table 2. Specific diagnosis: concordance of CNB and SE results (N = 71)

CNB results	Histopathologic result of subsequent excision specimen						
	IDP	Papillomas with ADH	Papilloma with DCIS	DCIS with papillary features / papillary DCIS	EPC	SPC	IBC with papillary features / IPC
IDP [a]	7	0	0	1	0	0	0
papillomas with ADH [b]	0	1	0	1	0	0	3
papillomas with DCIS [c]	0	0	0	0	0	0	0
DCIS with papillary features / papillary DCIS	0	0	0	9	0	0	6
EPC [d]	0	0	0	0	0	0	3
SPC [e]	0	0	0	1	0	0	0
IBC [f] ***papillary features / IPC*** [g]	0	0	0	0	0	0	39

a = benign intraductal papilloma
b = atypical ductal hyperplasia
c = ductal carcinoma in situ
d = encapsulated papillary carcinoma
e = solid papillary carcinoma
f = invasive breast carcinoma
g = invasive papillary carcinoma

Table 3. Clinical significance: concordance of CNB and SE results (n=71)

CNB results	Histopathologic result of subsequent excision specimen		
	Benign	Atypical	Malignant
Benign	7	1	1
Atypical	0	0	4
Malignant	0	0	58

Table 4. Summary of upgrade and concordance rates

Overall upgrade rate	8.45%
Overall concordance rate	91.55%
Concordance Rate for Specific Diagnosis	78.87%

Table 5. Predictive factors associated with upgrade of lesion on subsequent excision (N = 71)

Characteristics	Upgrade		Crude OR (95% CI)	*P* value
	Yes	No		
Age (in years)	N (%)			
<55	2 (8)	24 (92)	Ref	Ref
≥55	4 (9)	41 (1)	1.06 (0.21-5.39)	0.942
History of breast cancer				
No	6 (9)	64 (91)	Ref	Ref
Yes	0	1 (100)	3.31 (0.12-89.74)	0.477
BIRADS score				
1,2, 3	0	11 (100)	Ref	Ref
4	6 (19)	26 (81)	5.64 (0.29-108.71)	0.252
5, 6	0	28 (100)	0.40 (0.01-21.58)	0.655
Core diameter (in cm), median	0.2 [IQR: 0.2-0.2]	0.2 [IQR: 0.2-0.2]	0.06 (0.00-3662.43)	0.611

Ref: Reference category

1.5 to 2 times higher incidence of breast cancer, and those with atypia are found to have a higher risk of 4.3 times than that of the general population.[6] As such, several groups and institutions have attempted to establish criteria for the consistent management of PBLs. Based on European guidelines, PBLs are classified under breast lesions of uncertain malignant potential (B3). Qualifiers such as IDP without atypia and IDP with atypia are considered prior to further management, resulting in either with vacuum assisted biopsy (VAB) or surgical excision, respectively.[13]

Continuity of the histological picture of a PBL is also considered. ADH and DCIS in PBLs are qualified by the extent of the atypia present within the sample. While CNBs, and indeed, VABs may be of aid in excising papillary lesions, the continuity and wholeness of the lesion is not guaranteed. Hence, for a more thorough examination of the PBL, surgical excision may be preferred in some cases.[33] However, agreement with a more uniform consensus on whether to proceed with SE has been nebulous at best, as different groups variably prefer conservative or aggressive management within and between institutions.

The findings in this study revealed that 6 of the 71 PBL samples included had a computed overall upgrade rate of 8.45% (95% CI: 3.16-17.49%) and fall within the range of several studies published previously. However, it must be noted that these studies have varying upgrade rates with no consistent values, ranging from 1.58% to 31%.[1,2,5,7-11,18-23,30,32,34-36] As such, the setting of a guideline for clinical and surgical management proves to be of some difficulty still.

It was found that 2 of the 9 (22%) of the benign PBLs had been upgraded in our study. One was noted as atypical, and the other as malignant. This is well beyond the upgrade found in several publications, where the range only values from 1.58% to 8.8%.[8,9] This can be accounted for by the smaller sample size this study has in comparison to those currently published. Of note, however, is that some studies have pointed out that some of their upgraded cases were seen to have more aggressive lesions in the periphery of the index lesion than the actual index lesion itself, as well as intralesional heterogeneity, thus raising the possibility of sampling error.[22,35] In theory, this may also explain the one sample diagnosed as SPC on CNB that was later to be found as papillary DCIS on SE.

For atypical PBLs, 4 of 4 (100%) were found to have been upgraded to a malignant PBL. This is inconsistent with other studies, where 27% to 30% of the samples with atypia were upgraded to malignant.[8,9,25,27] Finally, all 58 malignant samples remained malignant, and hence classified as no upgrade. This is in keeping with other studies citing at least an 80.2% to 100% concordance rate for the diagnosis of malignant lesions from their initial CNBs in comparison with their excisions.[32,27] Consequently, the overall concordance rate in our study was found to be 91.55%, similar to the findings of a study by Fuentes et al (88.7%).[37]

An attempt to describe the concordance of the specific CNB and its respective excision diagnosis was made in this study, regardless of the clinical significance. It was of interest to the researchers to evaluate if at least the *sameness* of the initial final diagnosis yielded any significant data that could be investigated. The concordance rate (Table 2) for this aspect of the study yielded a result of 78.87%. This is comparative to a ten-year study where B3 lesions underwent CNBs, with a concordance rate of 83.3%[38] upon SE.

The demographics of this study showed a median age of 58.2 ± 14.1, 63% (45 of 63 patients) of which were older than 55 years of age. While not significant in our study, older patients, particularly those considered post-menopausal[27] and/or ≥55 years of age, were found to be associated with an upgrade in diagnosis.[1,10,21,23,28] A Turkish study recommended an even lower cut off, at 40 years of age.[11]

History of breast cancer was a predictive factor of interest in our study. Unfortunately, of the 71 included samples, only 1 had a previous personal history of invasive breast carcinoma, of which the CNB and SE revealed the same diagnosis. In larger studies such as those of Albert-Oller et al.,[29] it was found that 32.5% of those with history of IBC did show an upgrade in diagnosis after SE. On the other hand, those with no personal history had an overall upgrade rate of 11.2% in diagnosis, of which only 0.8% upgraded to a malignancy. Here, they suggest that even if the CNB was not suggestive of atypia, the personal history of IBC alone might suggest further management with SE. Chen and colleagues also had similar findings, where presence of atypia resulted in an upgrade rate of 27%; further, when paired with personal history of breast carcinoma, this was increased to 31%. Timing of the history was not significant

(i.e., recently as less than 1 year, or more than 1 year), suggesting history alone would suffice.[26]

BI-RADS score also did not yield any significant association with the upgrade rate in our study. However, it should be noted that those assigned BI-RADS 4 on imaging, 19% (6 of 32 samples) did show an upgrade in diagnosis. Those grouped as BI-RADS 1, 2, and 3, and BI-RADS 5 and 6 showed no samples having any change in their clinical significance. Upon review, some studies also did not show any significance in association with BI-RADS score. Yet, descriptively speaking, in the same instance, Salisbury et al.,[1] stated that lesions categorized as BI-RADS 4 were still likely to receive an upgrade. Other publications have found that a higher BI-RADS score, most those of 4c and 5, did show an upgrade in clinical significance.[7,10,22,35]

Core diameters in many studies have varied,[18] most using the gauge 14 size as a standard in their medical centers. In a meta-analysis by Zhang et al.,[22] wider core gauges such as those of vacuum assisted breast biopsies (VAB) were found to be able to identify PBLs with atypia better than those of the standard CNB. This led to a lower upgrade rate when performing VAB over CNB, as a thicker core diameter yields more tissue. In contrast, a ten-year single-center study found no significant difference in needle gauges in the underestimation of malignancy.[38] The latter study compares to ours, in that no association was found between core diameter and upgrade rate.

Admittedly, the small sample size of this study is a glaring limitation. Examination of the incidental findings from our data may shed some light as to why many samples were excluded from the final data analysis. A total of 184 patients with PBLs on CNB were initially recorded, of which 113 (61%) did not undergo subsequent SE. When stratified based on clinical significance, 62 of 71 (87%) of benign lesions, 19 of 23 (83%) of atypical lesions, and 32 of 90 (36%) of malignant lesions did not have any data on SE.

There is evidence that suggests that benign PBLs less than 1 cm may not warrant an excision.[1,13,16,21,22,28,39,40] A publication by Ko et al.,[39] found that their overall upgrade rate to a malignancy was only 2.3% in small, solitary, PBLs. Some have agreed that recommending close clinical follow-up instead of SE with these studies in mind. Despite these findings, not all publications agree. Glenn et al.,[34] and the American Society of Breast Surgeons[14] recommend surgical excision of the papillary lesions, regardless of size, arguing there is no safe limit at which papillomas could be managed with observation.

Unfortunately, data on the exact size of the PBLs in this study were not always available, hence, it was not included as a predictive factor. Instead, we noted 62 patients with a histopathological diagnosis of a benign PBL without atypia (i.e., intraductal papillomas) on CNB may have been recommended by their respective clinicians to be conservatively managed by close clinical follow-up. This is consistent with many studies recommending the same.[8,10,25,27,39,40] The remaining patients with an atypical or malignant diagnosis, however, are more likely to have been lost to follow-up in our center.

Circling back, a similar conundrum of the lack of lesion size was encountered by Khan et al. Instead, crediting to the 15-year length of their study, they were able to generate findings showing 10-year cancer free survival rates of PBLs without atypia (93.80%) and those with atypia (77.4%).[25] Extending the study period within our medical center may be of some merit if the investigators were to follow this example.

Regarding clinical significance of the diagnosis, our study grouped PBLs into three main groups, namely benign, atypical, and malignant. As observed during data collection, signed out surgical pathology reports for CNBs may state that a PBL in a specific sample could only be diagnosed as an atypical lesion at most. Recommendations for further immunohistochemical staining or an excision may or may not be stated in addition to the diagnosis. Yet it remains that the specific sample was insufficient to diagnose it as firmly benign or malignant with the data at hand at the time.[5] The sometimes fragmented or infarcted nature of a PBL in biopsy samples may account for this; and in rare instances, sampling error and cellular paucity of the sample further increases the difficulty at arriving at a more definite diagnosis.[18] As noted by Petrolla et al., the exercise of caution in diagnosis in accounting for the aforementioned confounding factors may also affect the upgrade rate.[37] Perhaps this may also account for the non-existence of the diagnosis of DCIS within a papilloma for our study, as some results opt to report this lesion as a whole as an "atypical papilloma." In addition to this, a literature review by Tay et al.,[17] found that the definitions for an upgrade in clinical significance differ in many studies, citing that one in particular did not actually consider atypia/ADH an upgrade, and thus may add to the inconsistencies in the body of literature available in the *uniformity* of what an upgrade is in the first place!

Limitations

As a retrospective study in a single center, selection bias must be accounted for. The exclusion of 113 samples from the initial 184 that was collected due to the patient not undergoing further surgical excision must also be raised as potential selection bias. During literature review, it was found that categorization was inconsistent across several publications. Some had opted to only include PBLs with or without atypia and excluding in-situ lesions and carcinoma altogether;[25] while others were more extensive, separating lesions based on radiologic-pathologic concordance or discordance.[38] The predictive factors selected for this research were also less in comparison to other investigations. Factors such physical palpability of a breast mass, radiologic size, radiologic-pathologic concordance/discordance, bloody nipple discharge, calcifications associated with or without a mass on imaging, location (central versus peripheral), core needle gauge, distance from the nipple, and family history of breast cancer were explored for any significant associations with an upgrade in clinical significance from their initial biopsies compared to their surgical resections.[13,16,21,27,29,40,41] The previously mentioned factors, then, can be included in future research endeavors.

Another limitation was found during the process of data collection. Our medical center is home to a number of different practitioners with varied exposures to international

and local training. In line with this is a possible difference among their own practices, and as such, may contribute to the differences in their style of management which may in turn reflect as to why some patients may be managed with or without an excision. In addition, perhaps the lack of data with regard to the patient's own decision to proceed with an excision and cosmetic concerns in relation to the clinician's medical advice were actually noted by Rizzo et al., to be a possible contributing factor that may be missed out as to why some are lost to follow-up.[18]

Racial diversity may be also of some interest for additional data input in the future. Noted by some authors, that inclusive of their limitations was that their studies skewed to one or another racial group, specifically African American or Caucasian women.[18,24] As our medical center caters to a more internationally diverse populace, it might be some benefit to include this as a predictive factor.

Previously mentioned is the lack of recording of lesion size. During the process of data collection, it was found that while the radiologic size was stated within the reports of the Breast Care Center, there was lack of consistency of measuring the PBL in surgical pathology reports. Most of the benign and atypical lesions were not measured, perhaps due to the inherent nature of PBLs' tendency for fragmentation during processing of a CNB.[18] Also, adding to this conundrum is the possibility of sampling in the form of fewer passes on CNB that may yield a smaller histologic sample for assessment.[24] Nevertheless, there might be value in recording the measurements of the PBLs on histomorphology moving forward.

Beyond the scope of this study was if IHCs were used to diagnose atypical PBLs on CNB, and if it had any impact for further surgical management. Though it is a fact that immunohistochemical markers have proven to be of utility in the diagnosis in differentiating among benign, atypical, and malignant PBLs,[1,2,4,29,37] there were only a few samples wherein IHCs had been performed to warrant investigation for the time period set (2020 to 2023) for this paper.

This study also raises the consistency of record keeping within the medical center. Not limited to the Institute of Pathology where the diverse ways patient data were kept and notated. Initially, we had considered *core gauge* instead of *core diameter* as a factor that may or may not have an association with a clinically significant upgrade in diagnosis. However, not all patient records had input the gauge or type of core used in performing the biopsy. Further, some core needle biopsies were not necessarily stated to be image guided – another interesting variable to be explored in future studies.

CONCLUSION

In conclusion, we found that the overall upgrade rate of our study was 8.45%. This is consistent with several publications. However, in part due to the small sample size, none of the predictive factors investigated showed any association with an upgrade in clinical significance in the diagnosis of PBLs. This is demonstrated by the wide confidence intervals computed during data analysis.

Despite this, of some benefit was this study revealed that there was a good concordance in diagnosis between CNB and SE within our center, revealing an overall concordance rate of 91.55% in terms of benign, atypical, and malignant PBLs. In assessing individual diagnoses of PBLs, the concordance rate was 78.87%. This suggests that there is merit to the reproducibility of results within our medical center.

The 4-year period of this study did impact on the sample size, and thus it is recommended to expand the time period in future endeavors. Also, exploring and collecting data, moving forward, on other predictive factors such as but not limited to lesion size, radio-pathologic concordance on lesion characteristics, and clinical symptoms is suggested, as this could potentially aid in adding to the current body of data in crafting standardized guidelines on how to manage patients with PBLs within our medical center and possibly for the Philippines.

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All authors certified fulfilment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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OPEN ACCESS – CASE REPORT

Infiltrative Basal Cell Carcinoma with Nodal Metastasis in a 74-year-old Female: A Case Report

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ABSTRACT

Basal cell carcinoma, the most common human malignancy, has a rare incidence of metastases ranging from 0.0028-0.55%. We report a case of a 74-year-old female with a 10-year history of an enlarging anterior thigh nodule. Wide resection and inguinal lymph node dissection revealed an infiltrative basal cell carcinoma with lymph node metastasis due to the presence of basaloid cells, limited peripheral palisading, loose stroma, extensive spread, perineural invasion and immunoreactivity to p40, BerEP4, and GATA3.

Key words: basal cell carcinoma, X-ray, squamous cell carcinoma in-situ, infiltrative basal cell carcinoma, basaloid cells

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common human malignancy and accounts for approximately 80% of all cancers of the skin. This condition is commonly seen in middle aged men and young women, and people with I-II Fitzpatrick skin phototype with sensitivity to ultraviolet (UV) radiation. Additionally, chronic exposure to arsenic, radiation treatment, and several congenital syndromes are also at risk for developing BCC. The pathogenesis of BCC involves genetic susceptibility compounded with sporadic UV exposure and eventual UV-induced mutations. The histomorphologic findings specific to this BCC subtype (infiltrative) include ulcerating or scar-like pink papules or plaque, variably sized nests of basaloid tumor cells infiltrating normal dermal collagen, and irregular permeating pattern of invasion at the deep tumor edge with possible perineural invasion. Immunoreactivity with BerEP4 is also desirable for the establishment of the diagnosis.[1-3]

CASE

We report a case of a 74-year-old female with a 10-year history of a palpable nodule on the anterior thigh. Consultation was done at a local hospital where surgery was advised. No other work-up, imaging, or intervention was done. In the interim, the nodule progressively enlarged. Three years prior to the present consult, ulceration of the mass was noted secondary to chronic scratching. No consultation was done. The patient treated this lesion by dressing the wound. The mass became fungating with purulent, foul-smelling discharge and occasional bleeding. A left thigh wedge biopsy was done at the Philippine General Hospital revealing a carcinoma in-situ (Figure 1).

Magnetic resonance imaging (MRI) revealed a lobulated mass involving the metaphyseal and diaphyseal portion of the distal femur with para-osseous soft tissue component and mass effects to the distal muscles of the anterior thigh, considerations were osteosarcoma or Ewing's

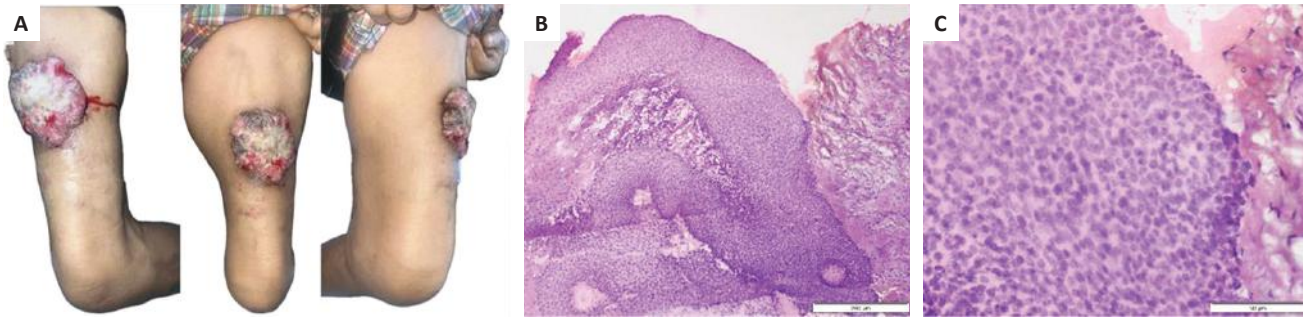

Figure 1. **(A)** 4 x 4 cm fungating, anterior thigh mass with areas of necrosis and punctate bleeding. Nest of tumor cells with large, irregular, hyperchromatic, pleomorphic nuclei, high nucleus to cytoplasm ratio, and mitotic figures described to be at least a carcinoma confined to the epidermis or a carcinoma in-situ **(B)** H&E, 100x; **(C)** H&E, 400x.

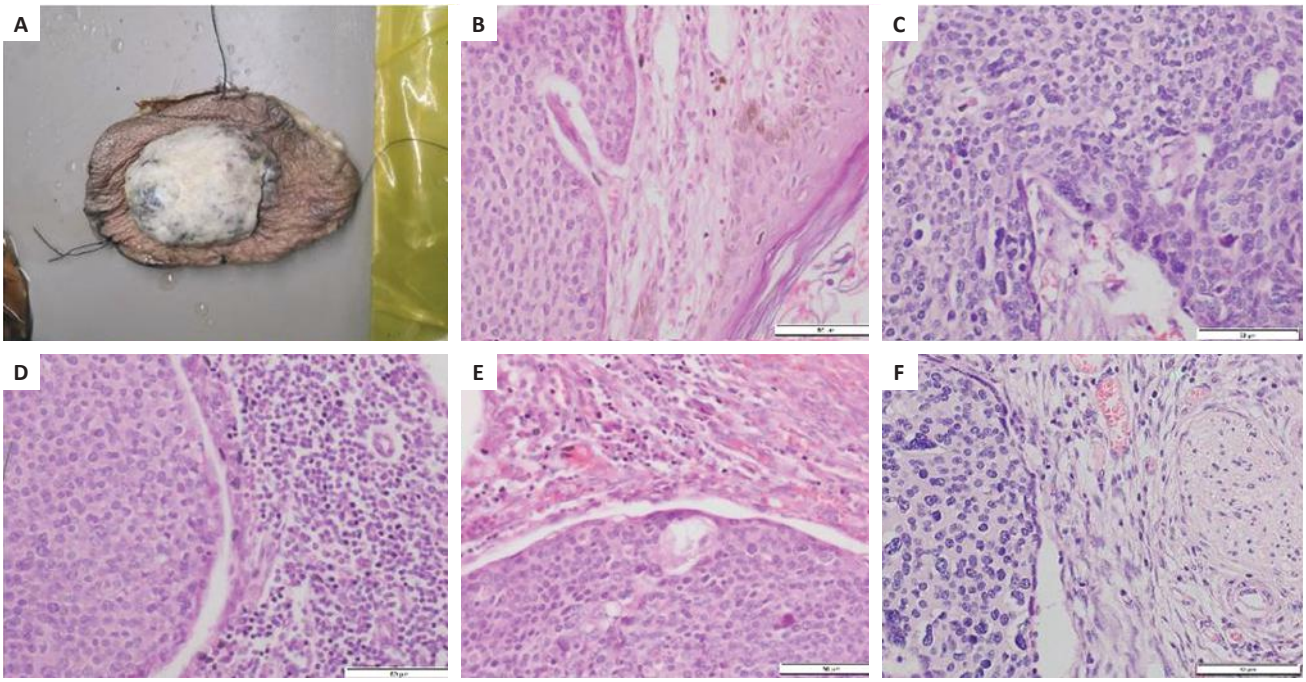

Figure 2. **(A)** Excised left anterior thigh mass. **(B)** H&E-stained high-power view or 400x magnification of the mass to skin. **(C)** H&E-stained high-power view or 400x magnification of the mass. **(D)** H&E-stained high-power view or 400x magnification of lymph node 1 with tumor cells. **(E)** H&E-stained high-power view or 400x magnification of lymph node 1 with tumor cells. **(F)** H&E-stained high-power view or 400x magnification of perineural invasion.

sarcoma. A day after, upon scratching, profuse bleeding of approximately one cup (250 mL) was noted, with associated pallor, dizziness, and loss of consciousness. A chest and abdominal CT scan revealed bilateral pulmonary nodules. On the day of admission, the patient presented with dizziness and five episodes of vomiting of previously ingested food. She underwent blood transfusion and was brought to the University of the Philippines-Philippine General Hospital. On physical examination, a 4 x 4 cm fungating left anterior thigh mass with areas of necrosis and punctate bleeding was noted (Figure 2). Additionally, a 2 x 1 cm lymph node was palpated at the left inguinal region. A wide resection of the anterior left thigh mass, with superficial inguinal lymph node dissection, split thickness skin grafting was performed. All margins were sent for frozen section and were evaluated as clear of tumor. The resection specimens were then processed for evaluation.

Histologically, the cells had large, irregular, hyperchromatic nuclei, prominent nuclear pleomorphism, high nucleus to cytoplasm ratio, and mitotic figures. This was then signed out as a malignant neoplasm, likely carcinoma, 8.3 cm in greatest tumor dimension, positive for skin ulceration and perineural invasion. There was tumor involvement in two out of twelve superficial inguinal lymph. Negative for tumor involvement in all surgical margins of resection. An immunohistochemistry panel of p40, BerEP4, and GATA3 was recommended for an initial panel (Figure 3). The immunohistochemistry results together with morphologic findings of small irregular clumps of basaloid cells, limited peripheral palisading, loose stroma, extensive spread, and perineural invasion can be seen and other essential characteristics present in the cells of interest favour a diagnosis of an infiltrative basal cell carcinoma (Figure 3).

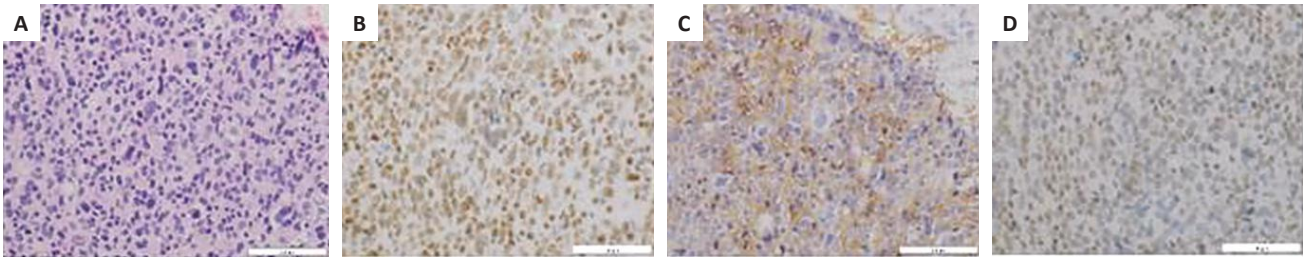

Figure 3. (A) H&E-stained high-power view or 400x magnification of malignant cells. **(B)** Immunohistochemistry study with p40 shows moderate, patchy, nuclear immunoreactivity under high-power view or 400x magnification. **(C)** BerEP4 shows moderate to strong, diffuse, cytoplasmic membranous immunoreactivity under high-power view or 400x magnification. **(D)** GATA3 shows moderate, focal, nuclear immunoreactivity under high-power view or 400x magnification.

Table 1. Differential diagnoses

Differentials	Morphology	CK5/6	BerEp4	P63	P40	BCL2	CD10	EMA	CEA	CK20
Basal cell carcinoma (and its subtypes)	Basophilic nucleus without a discernible nucleolus and scanty cytoplasm arranged in nests without keratinization. Stromal changes may be present, from a fibromyxoid change to retraction due to deposits.[10]	+	+	+	+	+	+	–	–	–
Basaloid follicular neoplasm	Trichoepthelioma and trichoblastoma are composed of basaloid cells which may have peripheral palisading, papillary mesenchymal bodies, and a loose to fibrotic stroma. A basaloid follicular hamartoma is composed of basaloid and squamoid cells that only arise where normal hair follicles are present with a loose, cellular or myxoid stroma and possibly with horns, cysts, and pigmentation.[11]	–	–	–	+	+	+	–	–	–
Basaloid squamous cell carcinoma	Increased N:C ratio, scant amphophilic cytoplasm, and oval and hyperchromatic nuclei without prominent nucleoli. Tumour islands exhibit basaloid cells with areas of comedo necrosis and focal keratinization.[12]	+	–	+	+	–	–	+	+	–
Sebaceous carcinoma	Sheets of atypical basaloid cells to sebocytes in sheets or lobules separated by fibrovascular stroma.[13]	–	–	–	–	–	–	+	–	–
Merkel cell carcinoma	Small round blue cell tumour with a high N:C ratio, round/oval nuclei, finely dispersed chromatin, indistinct nucleoli and scant cytoplasm.[14]	–	–	–	–	–	–	–	–	+

DISCUSSION

Basal cell carcinoma (BCC) is a carcinoma that arises from the interfollicular or follicular epithelium and is the most common skin malignancy worldwide. The incidence of this condition is inversely related to a country's geographic latitude combined with the pigment status of its inhabitants, with Australia having the highest incidence worldwide.[3] The risk of developing BCC increases with age and shows a predilection for elderly men and young women. The latter is attributed to the use of indoor tanning machines and better health seeking behaviour. Other risk factors include exposure to intense ultraviolet radiation, chronic arsenic exposure, radiation treatment in the young. All patients with Gorlin syndrome develop BCC and people with xeroderma pigmentosum, Bazex-Dupre-Christol syndrome and Rombo syndrome are also at risk of developing BCC.[4,5] The genes that regulate melanin production, *MC1R*, *ASIP* and *TYR*, if with polymorphisms, increase the risk of BCC.[6] This disease is brought about by an interplay of genetic variables and ultraviolet induced mutations. 58-69 % of sporadic cases of BCC are due to the loss of heterozygosity in the *PTCH1* gene. *TP53* gene alterations (loss of heterozygosity) can also be seen in 40-65% of sporadic cases and is due to *PTCH1*, leading to a dysregulation in cell cycle arrest, apoptosis, and DNA repair.[7]

Clinically, mostly in the head or neck, this may present as pink papules and plaques that would frequently ulcerate which would then present as a scar-like lesion. Metastasis is an extremely rare finding observed in approximately 0.003% to 0.5% of all cases reported.[8] A study done in America noted eleven cases of metastatic BCC from 2005 to 2018, 8 of which were infiltrative basal cell carcinoma.[9] Another study done in Brazil used data from 1894 to 2017 with a total of 389 cases of metastatic BCC with 178 or 45% of these manifesting with lymph node metastasis.[10] There are no noted cases of metastatic basal cell carcinoma in the Philippines as of now. Several risk factors have been proposed to be associated to metastasizing BCC such as large tumor size, deep invasion, repeated local recurrence, the infiltrative subtype with presence of perineural or perivascular invasion, history of radiation, location in the central portion of the face or ears, long period of evolution, squamatisation, and possibly immunosuppression.[9,10] The pathways of tumor metastasis are lymphatic or hematogenic wherein the most common site of metastasis is the lymph nodes followed by the lungs.[10] Histologically, all types of BCC display basaloid tumor cells with a hyperchromatic nuclei and scant cytoplasm. These tumor cells may vary in size and shape, and apoptotic cells may also be seen within the nests. Stromal changes range from a fibromyxoid change to the retraction of nests from stroma, calcification, and amyloid deposition. For the Infiltrative subtype as shown in this case, variably sized, jagged nests of basaloid

tumor cells would be seen infiltrating the normal dermal collagen in an irregular permeating pattern at the deep tumor edge with or without perineural invasion.[2,8]

Immunohistochemical staining is a useful tool in differentiating BCC from the differential diagnoses. BCC expresses p40, p63, and CK5/6, strongly. For BCL2 and CD10, BCC would have a diffuse positivity as well as a focal expression of AR. Negative stains that would rule BCC out from the other differentials are EMA, CEA, and CK20. For the next differential, basaloid follicular neoplasm, this would stain positive in CK20, stromal CD10, and peripheral BCL2. Basaloid squamous cell carcinoma would stain positive in EMA, p40, p63, CEA and negative for BerEP4. Sebaceous carcinoma would stain positive in EMA and negative in BerEP4. Merkel cell carcinoma would be diffusely positive in CK20 with a perinuclear dot-like positivity and would also stain diffusely in neuroendocrine markers.

Surgery and radiotherapy are the most common modalities. But since 2012, a more specific therapeutic modality emerged for patients that are not candidates for surgery or radiotherapy in the form of the inhibitors of the Hedgehog signalling pathways (Vismodegib and Sonidegib). They, however, are associated with a low tolerability and high rate of adverse events such as muscle spasms, dysgeusia, weight loss, alopecia, and fatigue. The rate of response to these therapeutic modalities for metastatic disease vary between 15% to 37%. Another immunotherapy agent was approved back in 2021 for patients with locally aggressive BCC that has not responded to Hedgehog inhibitors or in patients with metastatic BCC in whom Hedgehog inhibitors are not appropriate, Cemiplimab. This drug targets the PD-1 (programmed cell death-1) receptor on T and B cells and demonstrated clinically meaningful antitumor activity, including durable responses, and an acceptable safety profile in patients with metastatic BCC who had disease progression on or intolerance to Hedgehog pathway inhibitor therapy.[10,15]

CONCLUSION

Basal cell carcinoma and its subtypes is a common disease entity usually associated with a PTCH1 mutation. The diagnosis is made by clinical information complemented with a histopathologic evaluation. Surgical excision is the treatment modality of choice. Though nodal metastasis of the basal cell carcinoma cells is an extremely rare occurrence, lymph node involvement should still be investigated if clinically and radiologically warranted.

ETHICAL CONSIDERATIONS

Patient consent was obtained before the submission of the manuscript.

STATEMENT OF AUTHORSHIP

All authors certified fulfilment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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OPEN ACCESS – CASE REPORT

Primary Bilateral Ovarian Choriocarcinoma in a 33-year-old, G3P3(3003) Female: A Case Report

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ABSTRACT

This is a case of a 33-year-old, G3P3(3003) female patient with a clinical presentation of vaginal bleeding associated with on and off hypogastric pain. The patient was diagnosed and managed as a case of tubo-ovarian abscess and subsequently underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO). Microscopic sections of both ovaries, however, showed dual population of tumor cells composed of medium-sized, mononucleated cells admixed with multinucleated giant cells with marked pleomorphism, extensive hemorrhage and necrosis. Immunohistochemistry studies using beta-hCG was diagnostic of ovarian choriocarcinoma, favoring non-gestational in origin. Classification of non-gestational choriocarcinoma (NGOC) was established using diagnostic criteria for NGOC established by Saito et al., and Mangla et al. DNA analysis, however, remains to be the gold-standard for differentiating between gestational (GOC) and non-gestational (NGOC) etiology.

Key words: choriocarcinoma, germ cell malignancy, ovary, non-gestational

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INTRODUCTION

Ovarian choriocarcinomas are highly aggressive form of ovarian malignancy composed of trophoblastic cells, which are broadly classified into gestational and non-gestational subtypes.[1–5] While gestational choriocarcinoma (GOC) arise from molar or ectopic pregnancies, non-gestational choriocarcinoma (NGOC) can develop independently within the ovary without prior gestational event, often arising from malignant germ cell tumors or high grade somatic carcinomas.[3,4,6] Both forms are exceedingly rare, with a reported prevalence of 1 in 5,335 ovarian pregnancies for gestational choriocarcinoma and 1 in 369 million ovarian carcinomas for non-gestational choriocarcinoma in Eastern countries.[6] Collectively, ovarian choriocarcinoma account for less than 5% of all ovarian malignancies in Western population[4] with prevalence of non-gestational origin at <1%.[7,8] In the Philippines, the prevalence of ovarian choriocarcinoma remains unknown due to its extreme rarity, with only seven documented cases reported locally.[9]

The clinical manifestations of these tumors are similar regardless of origin, often nonspecific, with most common symptoms being abnormal vaginal bleeding in 89-97% of cases, and abdominal or pelvic pain in 39-54%.[2-5] Adult patients may present with symptoms related to ectopic pregnancy, whereas prepubertal children, may present with symptoms of precocious puberty.[2,3,6,7,10] The nonspecific nature of these symptoms may ultimately lead to a misdiagnosis preoperatively.[4] A markedly elevated serum β-hCG levels may aid clinicians in the diagnosis.[11]

Imaging studies using transvaginal ultrasound may yield nonspecific results while pelvic ultrasound may show highly vascular, echogenic non-homogenous mass with a normal uterus. Further imaging studies using CT scans may aid in evaluating the disease and determine presence of other hemorrhagic lesions.[7]

Grossly, ovarian choriocarcinomas typically present as unilateral, large, solid, hemorrhagic masses with extensive necrosis,[2,9] and bilateral ovarian involvement are exceedingly rare occurrence.[7] Histologically, these tumors are composed of mononucleated trophoblastic cells (cytotrophoblasts and intermediate trophoblasts) with clear cytoplasm, admixed with multinucleated syncytiotrophoblastic cells characterized by bizarre nuclei and abundant amphophilic cytoplasm. Tumor cells frequently form solid sheets and may occur as pure choriocarcinomas or in combination with other germ cell elements.[1-3,5,9,10] In the event of a mixed histology, the other germ cell elements typically surround the choriocarcinomatous elements resulting in small nodules that are associated with hemorrhage,[2] a feature that is not observed in this case.

Immunohistochemistry staining with beta-hCG, may provide a definitive diagnosis of choriocarcinoma.[1,2] Other IHC studies with CD30, PLAP, SALL4 and AFP may also aid in demonstrating the presence of other germ cell elements.[7]

Identification of these tumors is of utmost importance due to its aggressive nature and high metastatic potential.[1–5] Furthermore, distinguishing these neoplasm between its origin is crucial due to the difference in prognosis, management approach and treatment outcomes with gestational choriocarcinoma (GOC) having a more favorable prognosis and response to treatment.[6,10] In contrast, non-gestational choriocarcinoma (NGOC) is associated with a higher metastatic potential, poorer prognosis and a more aggressive clinical course, often requiring multi-drug therapy.[3,7]

This case report underscores the critical need to maintain an index of suspicion for malignant etiologies, even in the face of benign clinical and radiological findings; and highlights the importance of employing appropriate ancillary studies, such as tumor markers, immunohistochemistry, and molecular studies, to accurately diagnose rare and aggressive malignant tumors. Moreover, this case exemplifies the challenges posed by diagnostic limitations in the practice of pathology in a resource-constrained setting.

CASE

This case involves a 33-year-old, G3P3(3003) female who presented with a chief complaint of vaginal bleeding four months prior to admission, accompanied by intermittent hypogastric pain. Persistence of symptoms prompted the patient for consult at the obstetrics and gynecology department.

Initial imaging study using transvaginal ultrasound revealed a 2.4 x 2.0 x 2.0 cm unilocular cyst containing low-level echogenic fluid with a reticular pattern, along with an adherent 6.8 x 4.9 x 5.45 cm complex mass, including a solid area measuring 5.8 x 4.8 x 3.7 cm. The ultrasound impression suggested a tubo-ovarian abscess.

A review of the patient's laboratory results showed a positive serum pregnancy test with elevated serum beta-hCG at 541,149.90 mIU/mL (reference range: 1.2–5.0 mIU/mL), cancer antigen 125 (CA-125) at 199 U/mL (reference range: 0–35 U/mL), and lactate dehydrogenase (LDH) at 361 U/L (reference range: 120–246 U/L). Other laboratory results were unremarkable.

The patient was admitted as a case of tubo-ovarian abscess and subsequently underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO).

On gross examination, a previously sectioned TAHBSO specimen (Figure 1) was received with a highly irregular, poorly defined adnexa and enlarged right and left ovaries measuring 8.5 x 7.5 x 5.5 cm and 5.0 x 5.0 x 2.5 cm, respectively. The cut section of both ovaries shows a dark-brown, heterogenous, solid, hemorrhagic cut surface with extensive necrosis. Fallopian tubes were unidentifiable grossly (Figure 2).

Microscopic sections of both ovaries revealed extensive hemorrhage and necrosis with tumor cells arranged in sheets, composed of medium-sized, mononucleated cells with open coarse chromatin and clear cytoplasm, admixed with multinucleated giant cells with abundant, vacuolated, somewhat basophilic cytoplasm with marked pleomorphism (Figure 3). Also observed were bizarre mitotic figures and increased mitotic activity. Gross and microscopic sections of the uterine cervix and uterine corpus were unremarkable.

The primary diagnosis for this case was ovarian choriocarcinoma, with the following differential diagnoses: high-grade serous carcinoma, high-grade endometrioid carcinoma, and malignant germ cell tumors.[2,12-14]

Immunohistochemical analyses demonstrated the following findings: strong, diffuse cytoplasmic expression of beta-hCG; strong, diffuse membranous expression of CK7 in neoplastic cells; focal positive cytoplasmic expression of inhibin; and focal, weak positive nuclear expression of SALL4. No expression was observed for p53, WT1, PAX8, ER, CD30, and AFP (Figure 4).

The strong, diffuse, cytoplasmic expression on beta-hCG confirms the trophoblastic composition of the neoplastic cells. This result is also supported by the focal positive expression of inhibin. The diffusely membranous expression of CK7 indicates that the tumor cells originated in the female genital tract.

The lack of observed expression using p53, WT1 and PAX8, on the other hand, rules out high-grade serous carcinoma as a diagnosis. High-grade endometrioid carcinoma was ruled out due to non-expression of neoplastic cells on PAX8 and ER. Furthermore, malignant germ cell tumor was also ruled out due to negative staining on CD30 and AFP, as well as weak, focal positive expression on SALL4. In a study by Mei et al., SALL4 exhibits strong expression in all cases of dysgerminoma, embryonal carcinoma, and yolk sac tumors, but only shows weak to focal staining in 1 out of 3 choriocarcinoma cases with no expression observed on the remaining 2 cases.[15,16]

Elevated serum beta-human chorionic gonadotropin (beta-hCG) levels are a hallmark of choriocarcinoma.[1-5,7,8] And

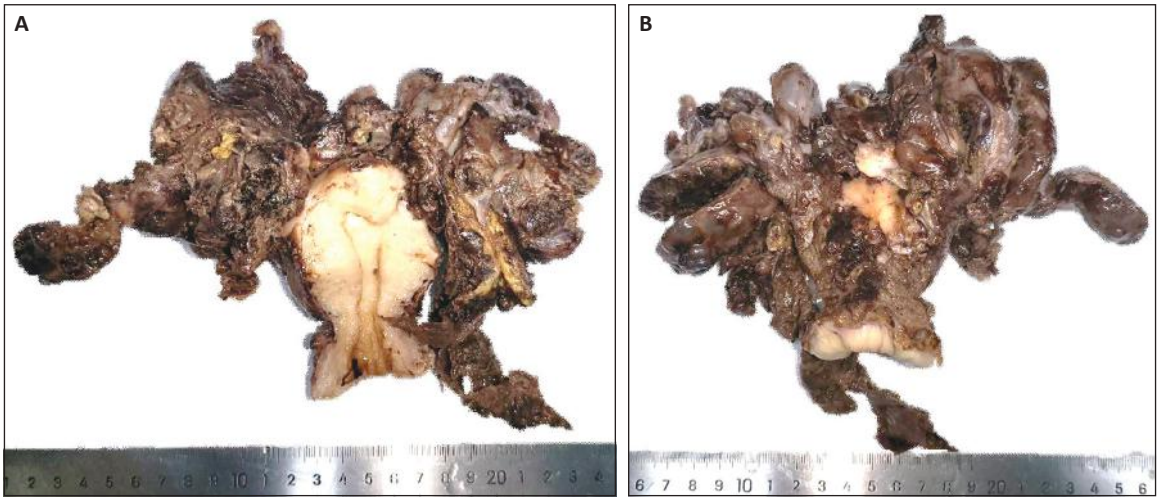

Figure 1. Gross appearance of the TAHBSO specimen. **(A)** Anterior view of the previously sectioned specimen with prominent bilateral hemorrhagic and irregularly enlarged adnexae. **(B)** Posterior view of the specimen.

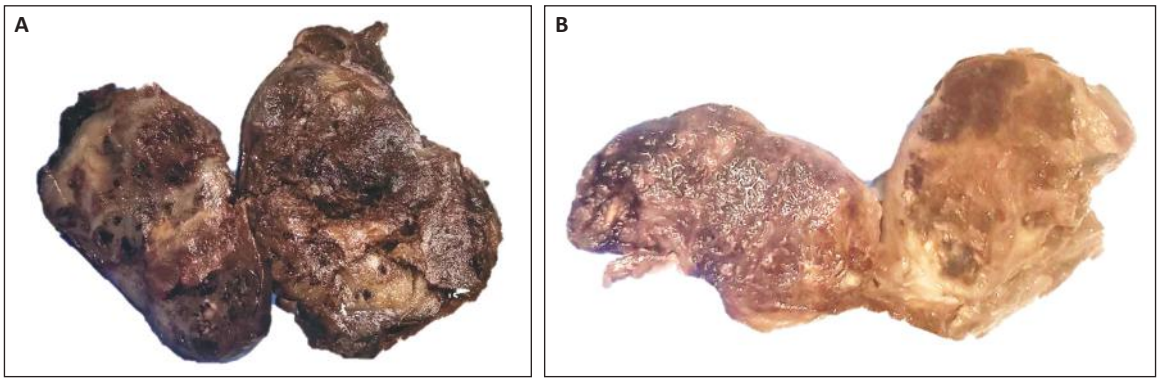

Figure 2. Cut sections of the right **(A)** and left **(B)** ovaries showing a dark-brown heterogenous, solid cut surface with extensive hemorrhage and necrosis.

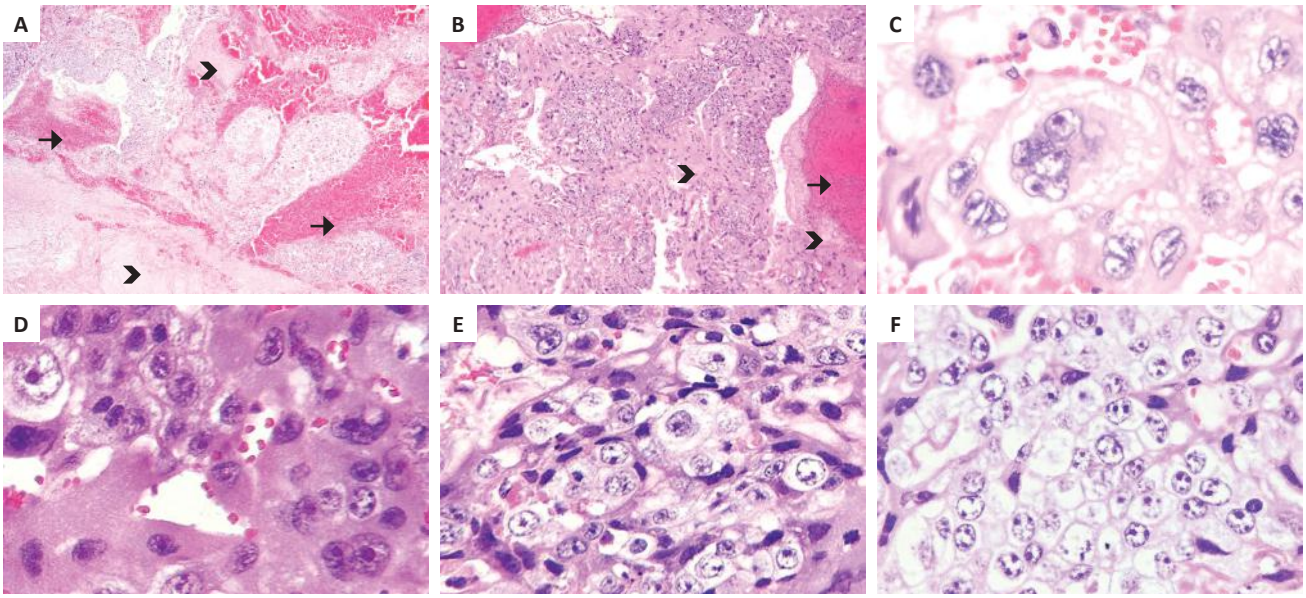

Figure 3. Representative microscopic sections of the right **(A, C, and E)** and left **(B, D, F)** ovaries, respectively. **(A)** and **(B)** show tumor cells in sheets with intervening extensive necrosis *(arrowhead)* and hemorrhage *(arrow)* (H&E, 40x). **(C)** and **(D)** show multinucleated cells with markedly pleomorphic nuclei, irregular cellular outline, open chromatin, prominent nucleoli and vacuolated, eosinophilic to amphophilic cytoplasm (H&E, 400x). **(E)** and **(F)** show medium-sized, mononucleated cells with open chromatin, prominent nucleoli, open chromatin and clear eosinophilic cytoplasm; also noted hyperchromatic nuclei and bizarre mitotic figures (H&E, 400x).

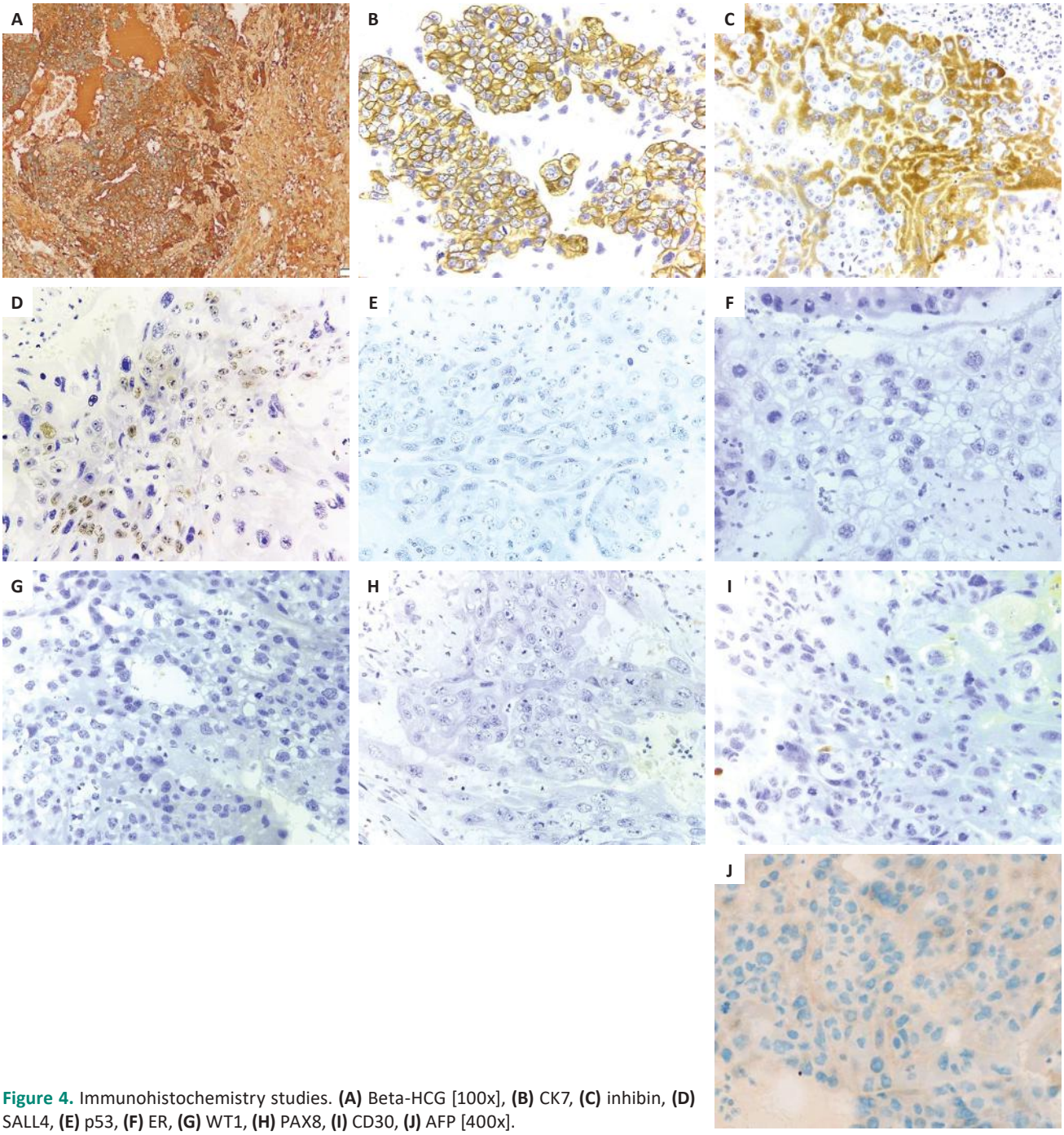

Figure 4. Immunohistochemistry studies. **(A)** Beta-HCG [100x], **(B)** CK7, **(C)** inhibin, **(D)** SALL4, **(E)** p53, **(F)** ER, **(G)** WT1, **(H)** PAX8, **(I)** CD30, **(J)** AFP [400x].

while this phenomenon may be observed in other ovarian malignancies, such as high-grade serous carcinoma,[13] dysgerminoma with syncytiotrophoblast, and embryonal carcinoma,[2] values exceeding 100,000 mIU/mL are highly suggestive of choriocarcinomatous etiology.[11]

Based on the careful consideration of the patient's clinical presentation, gross findings of the specimen, histomorphologic features and immune profile, a diagnosis of bilateral ovarian choriocarcinoma was established.

A metastatic work-up was conducted after the release of the final immunohistochemistry results using CT-scan showing no other lesion or mass, radiographically, indicating that the tumor is primary ovarian in nature. The patient was scheduled for completion surgery and further management; however, the patient was lost to follow-up.

Another dilemma posed by this case was the classification between gestational and non-gestational etiology, due to current unavailability of DNA analysis in the country. Nevertheless, this case most likely favors non-gestational etiology, due to the following salient features: no past or present history of abortion, molar or ectopic pregnancy, absence of corpus luteum microscopically, absence of disease in the uterus and other parts of the female genital tract, absence of neoplasm in the midline structures and the absence of other somatic malignancies.

DISCUSSION

Non-gestational choriocarcinoma is an exceedingly rare ovarian malignancy accounting for less than 0.6% of malignant ovarian germ cell tumors[7] and less than 1% of all ovarian neoplasm.[8] Gestational and non-gestational choriocarcinomas share identical histomorphologic features, clinical presentations, and immuno-profiles, making the differentiation between the subtypes a diagnostic conundrum. Detection of a corpus luteum microscopically, can aid in diagnosis, wherein, when observed, indicates the tumor to be of gestational in origin,[6,7,10] meanwhile, absence of trophoblasts in the uterus is suggestive of non-gestational origin.[5] Other factors to consider are the age of onset, history of molar pregnancy, history of ectopic or presence of current intrauterine pregnancy.[5-7,10]

Non-gestational choriocarcinoma is more likely to occur in prepubertal children, younger reproductive age women,[7] or postmenopausal women[2] with a mean age of diagnosis at 12 to 25 years old.[7] Distinguishing GOC and NGOC in women in reproductive age, however, may be considerably difficult, given the sexual and obstetric history.[2,7]

To further aid in distinguishing the origin of these tumors, a diagnostic criteria was established, by Saito et al., in 1963[17] based on the patient's detailed history, as follows: (1) absence of disease in the uterine cavity; (2) pathological confirmation of choriocarcinoma with the persistence of elevation in beta-HCG; (3) exclusion of history or current diagnosis of molar pregnancy; and (4) exclusion of coexisting intrauterine pregnancy.[7] This diagnostic framework was further expanded by Mangla et al., in 2023.[3] In Mangla et al.,'s criteria, germ cell origins were further classified into gonadal and extra-gonadal tumors. The criteria for gonadal or primary ovarian tumors shared similar criteria to those established by Saito et al., while extra-gonadal tumors, which are typically found to arise from midline structures have the following minimum diagnostic criteria: 1) radiographic evidence of a midline tumor; 2) no prior history of ovarian malignancy; and 3) elevated serum beta-hCG levels. Additionally, Mangla et al., also included criteria to determine non-germ cell origins arising from other somatic malignancies, as follows: 1) the presence of malignancy in other parenchymal locations, including the lungs, liver, or uterus, and 2) pathologic confirmation of a somatic malignancy (Figure 5).

The exact pathogenesis of ovarian choriocarcinoma remains unclear;[3,4,16] however, recent studies have identified specific genetic alterations. In gestational choriocarcinoma, overexpression of *TP53*, *CDKN1A*, *RB1*, *EGFR*, *ERBB2*, *c-MYC*, *BCL2*, *NANOG*, and *H19* genes has been observed, along with downregulation of *NECC1*, *TIMP3*, *DOC-2/hDab2*, *RASSF1A*, *CDKN2A*, *CDH1*, *IGF2*, *OCT4*, and *SOX2*. Additionally, genetic aberrations such as deletion of 7p12–7q11.2, amplification of 7q21–q31, and loss of 8p12–21 have been implicated. In contrast, non-gestational choriocarcinoma is associated with gain of 12p and overexpression of *p53*, *CGB5*, *CGA*, *NANOG*, *STELLA*, and *GDF3* genes.[3,7,18-20] Another study showed variations in the copy number, as well as significant amplifications of Her2, IKZF3, PGAP2 and c-Myc, in non-gestational ovarian choriocarcinoma which are not demonstrated in the gestational counterpart. These genes are believed to cause poorer immunogenicity of NGOC, contributing to a poor response to chemotherapy.[9]

Non-gestational choriocarcinoma is associated with a poorer prognosis and a more aggressive clinical course, often requiring multi-drug therapy.[3] Due to the aggressive nature and rapid growth of NGOC, metastasis occurs early. A review of 39 NGOC cases showed that 80% of patients had metastasis to the lungs, 30% to the pelvis, 20% to the vagina, and 10% to the liver. Furthermore, the overall survival rate of NGOC significantly drops to 25% over 3 years at FIGO stage IV compared to 100% for FIGO stages I, II and III.[7] Nevertheless, chemotherapy regimens containing cisplatin, such as the combination of cisplatin, etoposide, and bleomycin (PEB), have shown promising improvements in survival and prognosis of non-gestational choriocarcinoma.[2,7]

While diagnostic criteria may aid in the diagnosis of NGOC, definitive differentiation between the origins relies on paternal DNA analysis.[1-5,7,8] In this case, however, due to the unavailability of DNA testing, both diagnostic criteria were utilized to determine this case to be Non-gestational, primary ovarian in origin.

CONCLUSION

This report examines a case of primary bilateral ovarian choriocarcinoma in a 33-year-old, G3P3(3003) female patient who was initially diagnosed and managed as a case of tubo-ovarian abscess and benign ovarian neoplasm.

This case presented a diagnostic dilemma due to its rarity and the discrepancy between clinical diagnosis and microscopic findings. The strong, diffuse cytoplasmic immunoreactivity of beta-hCG confirms the trophoblastic composition of the neoplastic cells establishing the diagnosis of ovarian choriocarcinoma. Due to the unavailability of paternal DNA analysis, the non-gestational origin was determined through a comprehensive review of the literature using diagnostic criteria established by Saito et al., and Mangla et al., Nonetheless, DNA testing remains to be the gold standard for the diagnosis of non-gestational ovarian choriocarcinoma, indicating a need for molecular advancement in the country.

This case further underscores the significance of histological assessment of surgical specimens and the utilization of different diagnostic modalities, alongside a comprehensive review of the relevant literature to establish a pathologic diagnosis.

ETHICAL CONSIDERATIONS

Patient consent was obtained before the submission of the manuscript.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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OPEN ACCESS – CASE REPORT

Atypical Metastatic Presentation of Sporadic Clear Cell Renal Cell Carcinoma: An Indolent Unilateral Intranasal Mass in a 60-year-old Male with Recurrent Epistaxis

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ABSTRACT

Renal cell carcinoma (RCC) is notorious for its propensity to metastasize even after a prolonged period of remission following nephrectomy. The metastatic spread can occur months or even years after initial treatment, which necessitates a heightened level of clinical awareness and vigilance in patients with a history of renal malignancy, particularly who present with new or unexplained nasal symptoms. Although RCC most commonly metastasize to the lungs, bones and liver, its involvement in the nasal cavity is exceedingly rare, posing significant diagnostic challenges due to the non-specific nature of symptoms. We describe a case of metastatic renal cell clear cell carcinoma presenting with recurrent epistaxis and unilateral nasal obstruction. Immunohistochemistry studies play a crucial role in confirming the diagnosis and ruling out potential differential diagnoses, along with a comprehensive clinical history of the patient.

Key words: clear cell renal cell carcinoma, metastasis, nasal cavity, epistaxis, intranasal mass

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INTRODUCTION

Metastatic renal cell carcinoma (RCC) is a malignant tumor that originates in the kidneys and is known for its propensity to spread to distant sites, often involving the lungs, bones, liver, and less commonly, the head and neck region. However, metastasis to the sinonasal cavity region is exceedingly rare and presents significant diagnostic challenges due to its indolent growth and non-specific symptoms, which may mimic benign sinonasal pathology. This case highlights the insidious nature of metastatic RCC, where misdiagnosis can result in delay and suboptimal treatment and management.

CASE REPORT

This is a case of a 60-year-old male who presented with a 6-year history of non-foul- smelling, unilateral rhinorrhea in the left nasal cavity, without accompanying symptoms such as epistaxis, nasal congestion, fever, cough, headache, anosmia or nasal obstruction. The patient tolerated the condition over time. However, 2 years before admission, symptoms persisted and were now associated with epistaxis occurring twice a month. Each episode involved approximately three cotton balls soaked in blood, but the patient continued to tolerate his condition. Symptoms persisted until 1 year before admission, the patient sought consult with an otorhinolaryngologist. Nasal endoscopy with punch biopsy was done which noted a friable, ill-defined, reddish to purple intranasal mass with whitish discharges obstructing the entire left nasal cavity (Figure 1).

Paranasal sinus CT scan was requested which revealed a solid mass in the left nasal cavity, measuring at least 3.0 x 2.1 x 4.3 cm. The mass deviated the nasal septum to the right and laterally obstructed the left ostiomeatal unit. Fluid densities were in the left ethmoid, sphenoid and maxillary sinus (Figure 2). However, the result of the initial

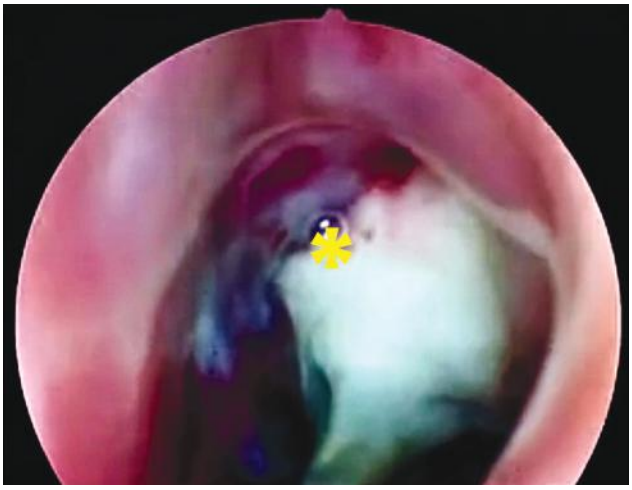

Figure 1. Nasal endoscopy findings showing a reddish intranasal mass (*) with whitish discharges.

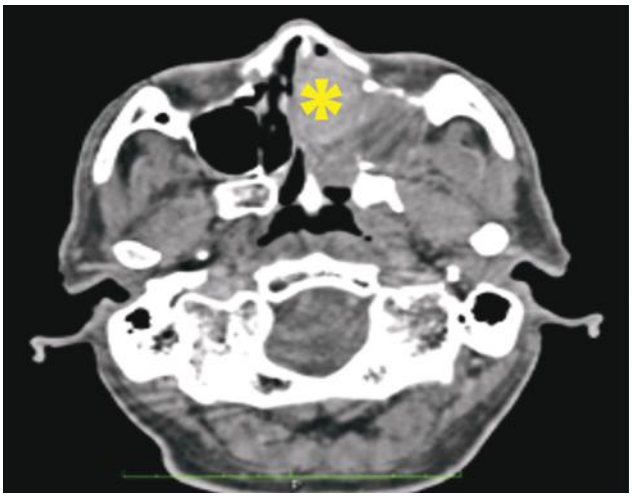

Figure 2. Paranasal sinus CT scan findings showing a solid mass in the left nasal cavity (*), deviating the nasal septum and obstructing the left ostiomeatal unit.

biopsy was non-diagnostic, which revealed only extensive necrosis with acute and chronic inflammation.

Repeat punch biopsy was done. The specimen submitted for pathology consists of three, minute, tan cream, irregular tissue fragments which measured 2.0 x 1.1 x 0.7 cm. Histopathologic examination showed tumor cells predominantly in tubular and microcystic architecture and some in an acinar pattern intervened by fibrous stroma (Figure 3 and 4). The tumor cells were relatively large, having irregularly ovoid, hyperchromatic, centrally located nuclei with inconspicuous nucleoli and abundant clear cytoplasm. Luminal polarization of nuclei was absent. The tumor cells in acinar pattern were separated by fibrotic stroma, characteristically endowed with a prominent network of small and thin-walled blood vessels (Figure 5). No areas demonstrated papillary or alveolar architectural patterns. Keratinization was not observed in any area.

Based on the histomorphologic features, main differential diagnoses include primary clear cell carcinoma of the

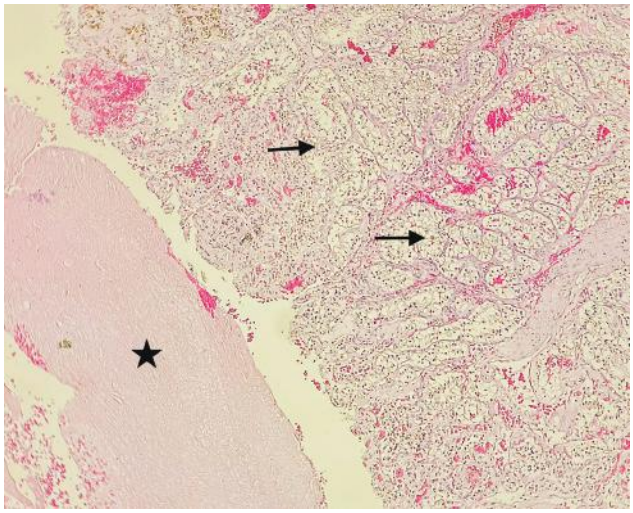

Figure 3. Tumor cells *(black arrows)* in tubular, microcystic and acinar architecture with extensive necrosis *(black star)* (H&E, 40x).

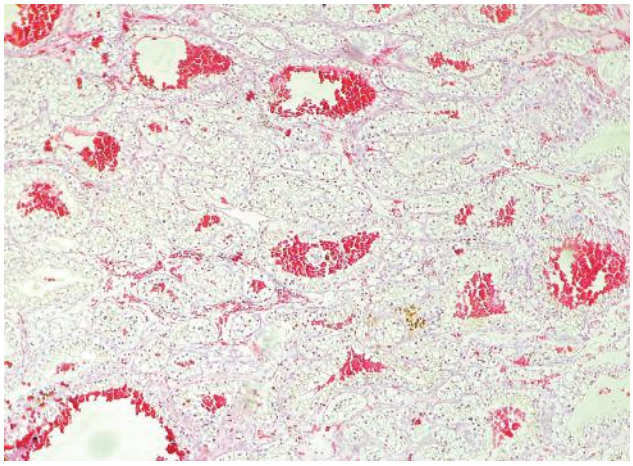

Figure 4. Tumor cells in prominent acinar growth pattern intervened with extravasated blood (H&E, 100x).

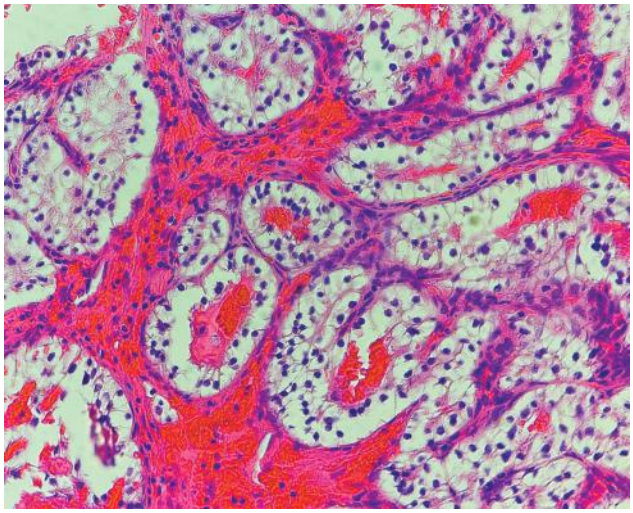

Figure 5. Tumor cells with centrally located nuclei and abundant clear cytoplasm (H&E, 400x).

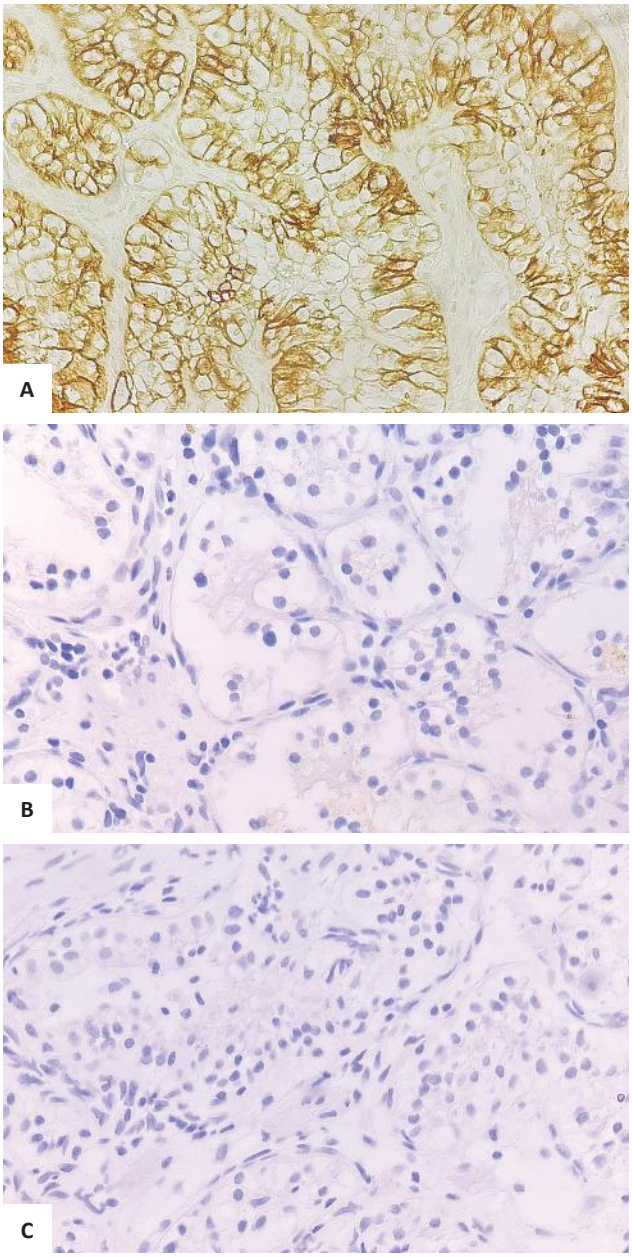

Figure 6. Immunohistochemistry showing strong and diffuse, **(A)** membranous staining for CK7; **(B)** negative for CK20 and **(C)** PSA.

nasal cavity, metastatic carcinoma from the prostate and thyroid (papillary carcinoma), and non-intestinal type, adenocarcinoma of clear-cell variant.

Initial panel of immunohistochemistry studies revealed negative for CK20 (Figure 6B), and PSA (Figure 6C). Tumor cells were positive for CK7 (Figure 6A). CK7 positivity and CK20 negativity suggested a primary of the lung, salivary gland, breast, or head and neck.

Additional immunohistochemical staining was performed, including S100, TTF-1, p63 and CD117. Negative staining for S100 (Figure 7A) and TTF-1 (Figure 7B) ruled out sinonasal mucosal malignant melanoma and metastatic papillary thyroid carcinoma respectively. The absence of p63 expression ruled out both squamous cell carcinoma

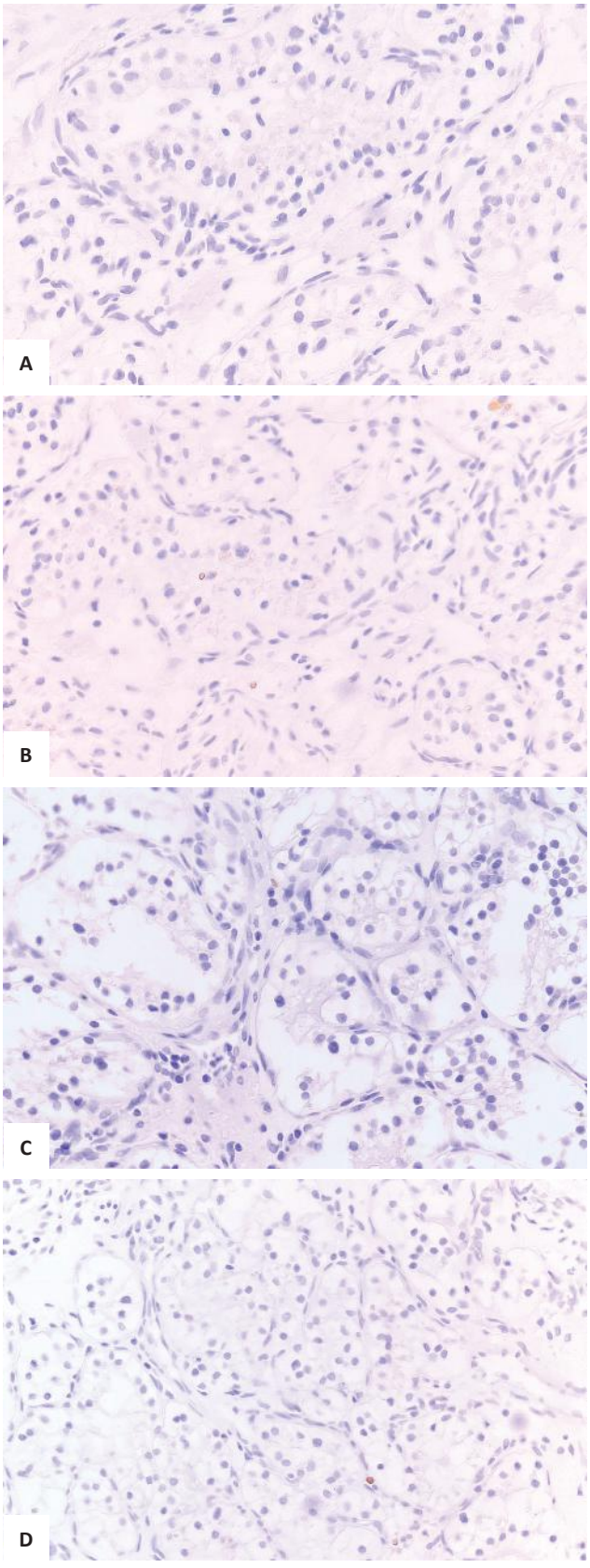

Figure 7. Immunohistochemistry showing negative expression for **(A)** S100, **(B)** TTF-1, **(C)** p63 and **(D)** CD117.

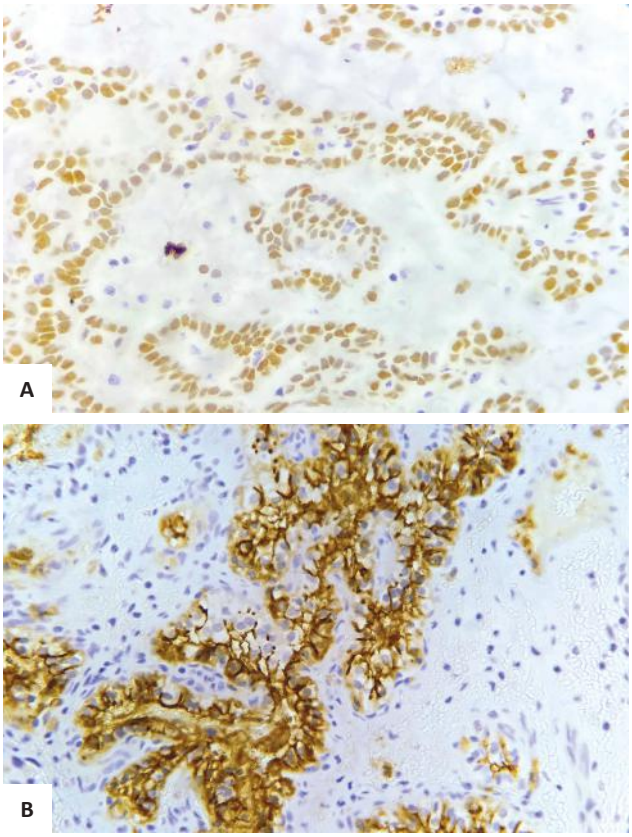

Figure 8. Immunohistochemistry showing strong and diffuse, **(A)** nuclear staining for PAX8 and **(B)** membranous staining for CD10.

of clear cell variant as well as mucoepidermoid carcinoma with clear cell changes (Figure 7C). Clear-cell predominant acinic cell carcinoma is also ruled out because of the absence of CD117 expression (Figure 7D).

Negative staining for S100 also ruled out myoepithelioma and myoepithelial carcinoma as potential diagnoses. Hence, the most likely remaining differential diagnosis is a metastatic lesion from a renal malignancy, which would typically exhibit CK7 positivity and CK20 negativity. While the immunoprofile is compatible with metastatic papillary renal cell carcinoma, it is not aligned with its histomorphologic characteristics. Hallmark features of papillary renal cell carcinoma such as presence of papillary architecture of tumor cells, clear and glycogenated cytoplasm, and 'piano key' appearance of aligned nuclei are absent.

A final panel of immunostains was performed such as PAX8 (Figure 8A) and CD10 (Figure 8B), showing strong nuclear and membranous positive staining, respectively. Upon reviewing the clinical history of the patient, he had undergone radical nephrectomy last 2014 at a private institution. CT urography confirmed a surgically absent right kidney, with no other significant findings. According to the patient, he had been diagnosed with Stage I, Renal Cell Carcinoma. Considering the histomorphologic features and immunoprofile in conjunction with the patient's clinical history, the case was signed out as Metastatic Clear Cell Carcinoma of the Kidney.

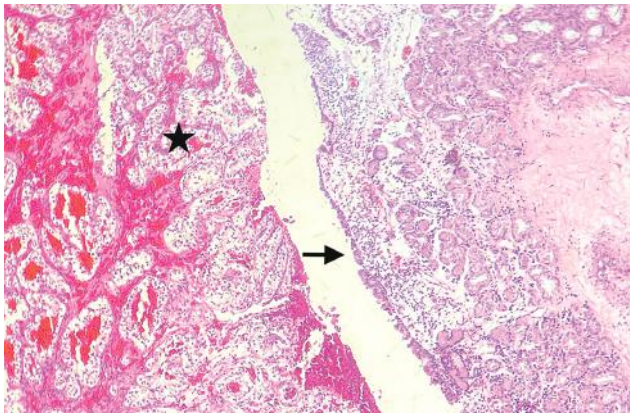

Figure 9. Tumor cells in prominent microcystic architecture intervened with extravasated blood *(black star)* and normal respiratory epithelium of the nasal cavity with mucosal glands *(black arrow)* (H&E, 40x).

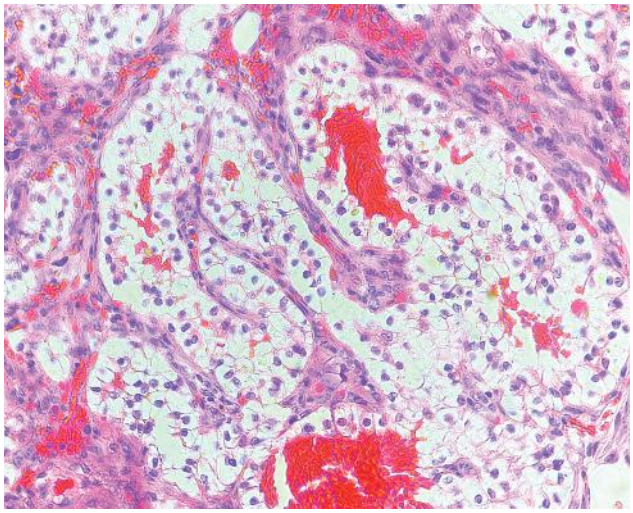

Figure 10. Tumor cells with centrally located nuclei and abundant clear cytoplasm (H&E, 400x).

The patient was advised for surgery but did not comply due to financial limitations. Approximately four months prior to admission, an increase in episodes of epistaxis was noted and prompted the patient to consult at our institution. The patient underwent endoscopic sinus surgery to excise the intranasal tumor. The specimen submitted for pathology consists of several, tan to dark brown, rubbery to firm, smooth to rough, irregular tissue fragments measuring 8.0 x 6.0 x 1.5 cm. Histopathologic examination revealed tumor cells in prominent microcystic architecture intervened by fibrous stroma and extravasated blood (Figure 9) with extensive necrosis (Figure 11). The tumor cells have centrally located nuclei with abundant clear cytoplasm (Figure 10). These findings were consistent with the previous punch biopsy of the nasal cavity. Immunostaining with CD10 on the received specimen was done to support the previous diagnosis of Metastatic Clear Cell Renal Cell Carcinoma, demonstrating strong positivity (Figure 12).

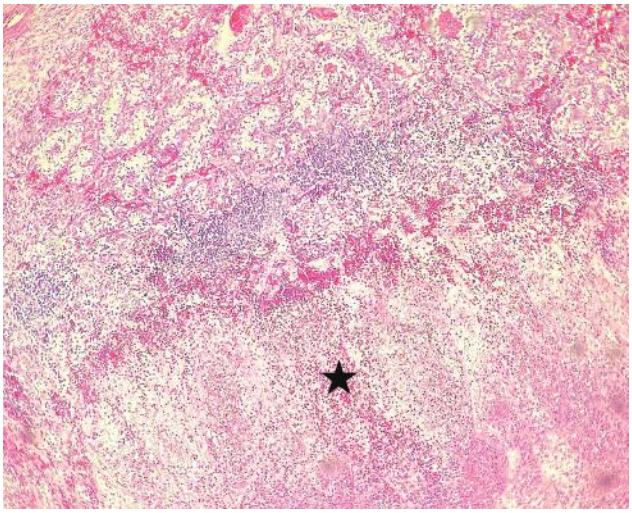

Figure 11. Tumor cells in a background of extensive necrosis *(black star)* (H&E, 100x).

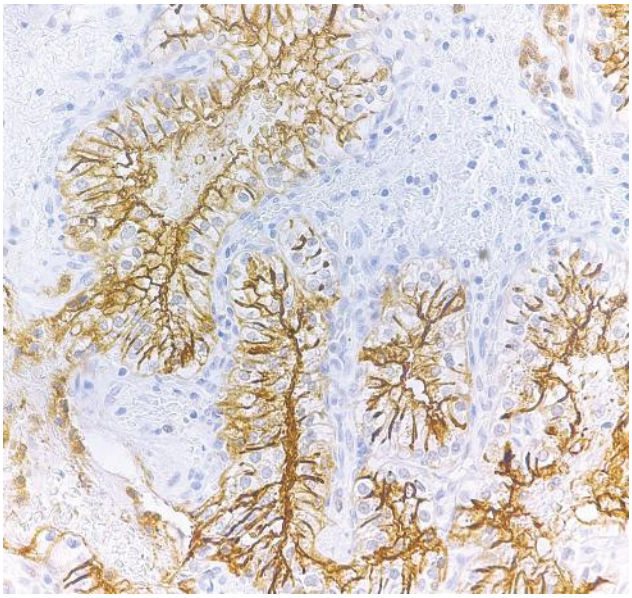

Figure 12. Immunohistochemistry showing strong, membranous staining with CD10.

DISCUSSION

Worldwide, renal cell carcinoma (RCC) represents the sixth most frequently diagnosed cancer in men, accounting 5% of all malignancies.[1] In the Philippines, a total of 2, 916 new cases of renal malignancy were recorded with a mortality of 1.3% last 2022. The 5-year prevalence of renal malignancy was 7.4 per 100, 000 population, highlighting its significant impact on the global burden of cancer. Approximately 30% of patients with renal cell carcinoma present with metastatic disease primarily in the lungs (75%), soft tissues (36%), bone (20%), liver (18%), cutaneous sites (8%) and CNS (8%). Metastasis to the paranasal sinuses and intranasal cavity is exceedingly rare.[2] This atypical site of metastasis is believed to occur through either hematogenous or lymphatic spread, although the exact mechanism remains uncertain.[3] Hematogenous dissemination is considered the most common route and may follow one of two pathways. The first pathway involves the renal vein, inferior vena cava, heart, lungs, and maxillary artery. This route is supported by the frequent presence of simultaneous lung and/or brain metastases in reported cases of RCC with sinonasal involvement.[4] The second and less common route is through the Batson's paravertebral venous plexus, which allows tumor cells to bypass filtration through the lungs, liver and brain.[5] Lymphatic spread is via the regional lymphatics and the thoracic duct.[6]

However, RCC is the most common cancer metastasizing to these regions based on published case reports.[7] Metastasis to these regions often presents with recurrent epistaxis. No published case report has been documented in the Philippines up to this date. Unfortunately, the prognosis of metastatic RCC is poor and often resistant to chemotherapy and radiotherapy.[8] Thus, immediate diagnosis is of great importance for better treatment outcomes. For isolated sinonasal metastasis from RCC, surgery is generally regarded as the treatment of choice. Endoscopic resection is appropriate for localized lesions. In cases of extensive sinonasal involvement, a maxillectomy may be warranted.[9] Others recommend the addition of radiotherapy to surgical management, though its efficacy has been reported with variable outcomes. It reduces the tumor burden and provides symptomatic relief.[10]

Immunohistochemistry studies are typically required to confirm the diagnosis. For this case, several immunostains such as CK7, CK20, PAX8, CD10, TTF-1, S100, PSA, p63 and CD117 were performed. Potential differential diagnoses must be ruled out such as primary clear cell carcinoma of the nasal cavity, squamous cell carcinoma of clear cell variant, clear cell-predominant acinic cell carcinoma, sinonasal mucosal malignant melanoma, mucoepidermoid carcinoma with clear cell changes, myoepithelioma, myoepithelial carcinoma, metastatic carcinoma from thyroid and kidney, as well as non-intestinal type adenocarcinoma of clear cell variant.

The prognosis for metastatic renal cell carcinoma remains poor; however, early and accurate diagnosis of metastatic disease can substantially improve the patient's survival rate. According to the existing literature, surgical excision of a solitary metastatic lesion following nephrectomy has been associated with a 41% survival rate at 2 years and a 13% survival rate at 5 years.[11] These findings highlight the potential benefit of early intervention in selected cases. In contrast, survival outcomes are notably worse when only the metastatic lesion is removed, as this approach alone significantly reduces long-term survival rates. Furthermore, patients with multiple metastatic lesions face a bleak prognosis, with reported five-year survival rates ranging from 0% to 7%. These statistics underscore the critical importance of early detection, accurate staging, and appropriate treatment strategies to improve outcomes for patients with metastatic RCC.[12]

CONCLUSION

The clinical progression of renal cell carcinoma (RCC) is highly variable, exhibiting a spectrum that ranges from an aggressive, rapidly advancing course to instances of

spontaneous regression. The metastatic potential of RCC is a significant concern, as metastasis may be detected in 25-30% of patients at the time of initial diagnosis. This can metastasize even years after nephrectomy, emphasizing the unpredictable nature of the disease. This delayed metastatic spread presents a challenge in monitoring patients' post-treatment, as metastases may emerge long after apparent clinical remission, underscoring the need for long-term surveillance and ongoing vigilance in managing patients with a history of RCC. Reporting these uncommon occurrences enhances clinical understanding, aids in the recognition of unusual metastatic patterns, and contributes valuable insights to the literature. This, in turn, helps refine diagnostic approaches and treatment strategies for similar future cases, fostering improved patient outcomes.

ETHICAL CONSIDERATIONS

Patient consent was obtained before the submission of the manuscript.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest

FUNDING SOURCE

None.

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24 March 2025

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Prevalence Of Inferred Clonal Hematopoiesis-Associated Genes In Patients With Solid Tumors Detected On Unpaired Next-Generation Sequencing Assays: A Single Center Experience In The Philippines

Presenter: Jeffrey D. Domingo, MD, DPSP

St. Luke's Medical Center - Quezon City

Review Of Encapsulated Follicular-Patterned Thyroid Neoplasms: An Institutional Study

Presenter: Cecile C. Dungog, MD, PhD, DPSP

Philippine General Hospital

Cytogenetic Profiles And Disease Surveillance Outcomes In Kappa And Lambda Restricted Plasma Cell Myelomas: A National Reference Laboratory Study

Presenter: Allison Kaye L. Pagarigan, MD, DPSP

The National Kidney and Transplant Institute

An Analytical Cross-Sectional Study On Upgrade Rate And Associated Predictive Factors Of Papillary Breast Lesions On Core Biopsy In A Private Tertiary Institution

Presenter: Nicole Dominique C. Santos, MD, DPSP

St. Luke's Medical Center - Global City

A Pilot Study On The Prevalence Of Viral And Bacterial Pathogens From Nasopharyngeal Swabs Using Multiplex Polymerase Chain Reaction Testing In A Tertiary Hospital

Presenter: Nathaniel Jan G. Tan, MD, DPSP

Makati Medical Center

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Poster Finalists

Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm (MiNEN) of the Cervix in a 38-Year-Old Female: A Case Report and Review of Literature

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Bilateral Non-Gestational Ovarian Choriocarcinoma in a 33-year-old Female, A Case Report

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Zamboanga City Medical Center

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National Kidney and Transplant Institute

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Invasive Breast Carcinoma with Pure Signet-Ring Cell Differentiation: A Case Report

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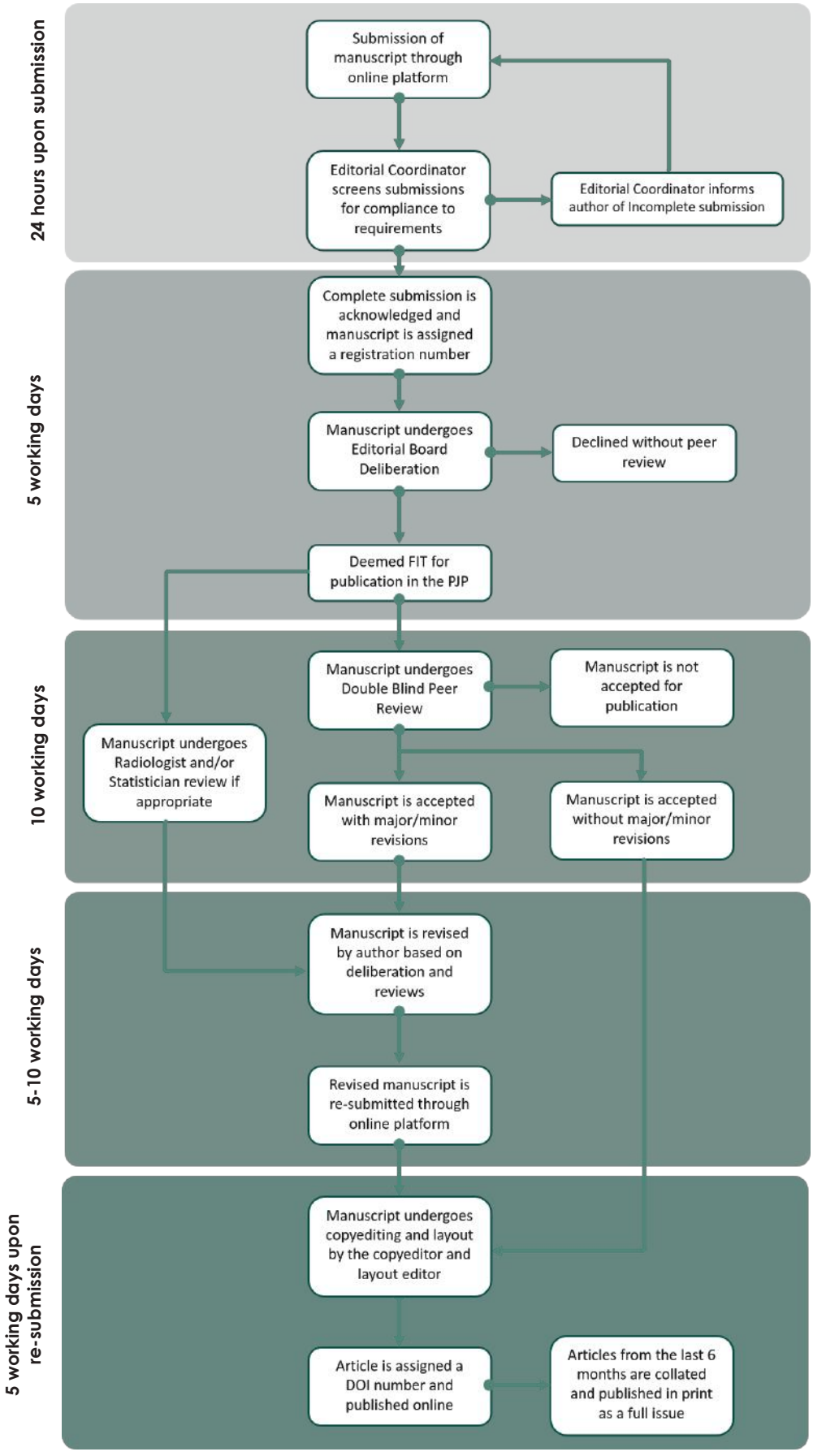

Figure 1. Editorial Process Flow.

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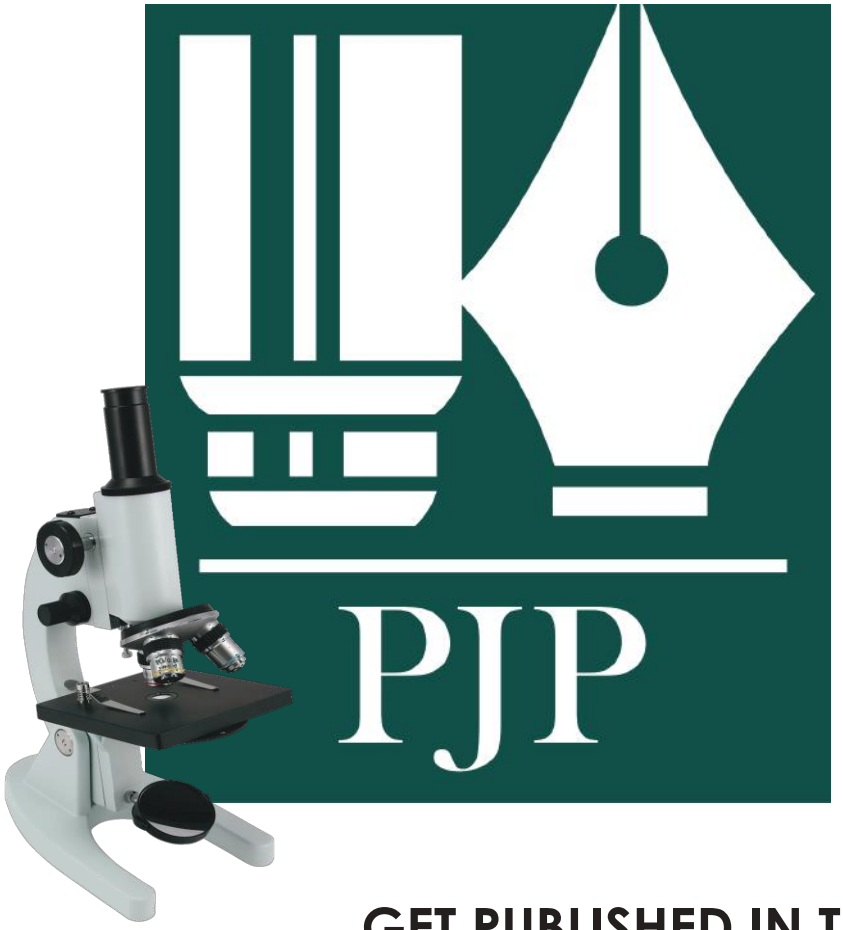

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