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Advancing the Understanding and Management of Blastic Plasmacytoid Dendritic Cell Neoplasm: Insights from Recent Case Studies

New Insights into BPDCN from Recent Case Studies

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Abstract

In this editorial, we provide commentary on the article "Blastic plasmacytoid dendritic cell neoplasm: Two case reports" by Yi-Qian Ma, published in the recent issue of the World Journal of Clinical Cases. We specifically discuss the mechanisms of the pathogenesis, diagnosis, and management of blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare but aggressive haematologic malignancy characterized by frequent skin manifestations and systemic dissemination. Yi-Qian Ma's article enriches our understanding of BPDCN through detailed case reports showing the clinical, immunophenotypic, and histopathological features that are critical for diagnosing this disease. These cases highlight the essential role of pathologists in employing advanced immunophenotyping techniques to accurately identify the disease early in its course and guide treatment decisions. Furthermore, we explore the implications of these findings for management strategies, emphasizing the use of targeted therapies such as tagraxofusp and the potential of allogeneic haematopoietic stem cell transplantation (allo-HSCT) in achieving remission. This editorial underscores the importance of interdisciplinary approaches in managing BPDCN, pointing towards a future where precision medicine could significantly improve patient outcomes.

Key Words: Blastic Plasmacytoid Dendritic Cell Neoplasm, Immunophenotyping, Targeted Therapies, Haematologic Malignancy, Pathogenesis

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Core Tip: This editorial revisits the pathogenesis, diagnosis, and innovative management strategies for blastic plasmacytoid dendritic cell neoplasm (BPDCN), inspired by recent case reports written by Yi-Qian Ma et al. It underscores the critical role of advanced immunophenotyping in early and accurate diagnosis and highlights

the promise of targeted therapies such as tagraxofusp and allogeneic haematopoietic stem cell transplantation (allo-HSCT) for improved outcomes. Emphasizing interdisciplinary collaboration, this work points towards precision medicine as a future paradigm, aiming to transform the management and prognosis of this aggressive haematologic malignancy, thereby paving the way for more effective patient-specific therapeutic strategies.

INTRODUCTION

1 Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive haematologic malignancy identified by the World Health Organization. BPDCN is characterized by immature cells differentiating into plasmacytoid dendritic cells, often leading to significant skin involvement and systemic spread. Previously known by various terms including blastic NK-cell lymphoma and agranular CD4 + CD56 + haematodermic neoplasm, BPDCN is now the preferred term to increase diagnostic precision[1, 2]. The disease typically presents with diverse, nonitchy skin lesions on the upper torso, head, neck, and limbs[3-5]. Some individuals display a leukaemic presentation, characterized by symptoms related to peripheral blood cytopenias, such as fatigue, bleeding or easy bruising, and recurrent infections, with lymphadenopathy also commonly noted at diagnosis[1, 2, 6].

The diagnosis of BPDCN, which occurs at a rate of approximately 0.04 cases per 100,000 people annually in the United States, is challenging because of its rare and nonspecific presentation[7]. This rarity demands a high degree of clinical suspicion and pathologic expertise for early and accurate identification. The disease arises from dormant plasmacytoid dendritic cells that exhibit abnormal activation of the NF- κ B pathway, among other molecular and cytogenetic anomalies[8, 9]. Typically, BPDCN cells are characterized by the expression of CD123 and TCF4, and lack lineage-specific markers, which helps differentiate BPDCN from other acute leukaemias[10].

Pathologists play a crucial role in the diagnosis and management of BPDCN, as they utilize immunophenotyping techniques to identify specific markers such as CD123,

CD4, and CD56. These markers are essential for confirming the diagnosis and informing treatment options. Prompt and precise diagnostic testing is critical, as it significantly impacts treatment decisions and patient outcomes, highlighting the necessity of collaboration between clinicians and pathologists in managing this complex disease.

Development and Functions of Plasmacytoid Dendritic Cells

Plasmacytoid dendritic cells (pDCs), the normal counterparts of BPDCN cells, originate from haematopoietic stem cells (HSCs) through a series of well-defined differentiation stages[11]. Initially, HSCs differentiate into common monocyte progenitors (cMoPs) and dendritic cell precursors (CDPs). From these CDPs, cells further evolve into either conventional dendritic cells (cDCs) or plasmacytoid dendritic cells (pDCs). Under certain conditions, monocytes from cMoPs can also develop into dendritic cells, forming part of the mononuclear phagocyte system[12].

Notably, pDCs are essential components of ³the innate immune system, because of their ability to produce large amounts of type I interferons (IFNs), which are key in fighting viral infections[13]. Although pDCs are traditionally thought to originate from myeloid progenitors such as cDCs, recent research has shown that a unique subset of pDCs may come from lymphoid progenitors[14-16]. These lymphoid-origin pDCs, referred to as "B-pDCs," not only share pathways with B cells but also exhibit unique gene expression and functions, including a reduced production of type I IFNs and an increased capacity for activating T cells[17].

Under normal physiological conditions, pDCs are predominantly found in the peripheral blood and secondary lymphoid organs and serve as vigilant sentinels against pathogens[18]. pDCs detect viral nucleic acids through toll-like receptors (TLRs), specifically TLR7 and TLR9, initiating the production of IFN- α and IFN- β [18, 19]. This potent IFN response not only curtails viral replication but also increases ²the activity of other immune cells such as natural killer (NK) cells and T cells, establishing a comprehensive antiviral defence[20]. Additionally, pDCs help maintain immune

balance by regulating the activity of conventional dendritic cells and moderating the immune response between proinflammatory and regulatory actions[18, 21].

Pathological and Molecular Features of BPDCN

Histopathologically, BPDCN is characterized by a diffuse infiltrative pattern primarily in the dermis and often the subcutaneous tissue, sparing the epidermis. BPDCN typically presents as a uniform population of medium-sized blastic cells with fine chromatin, inconspicuous nucleoli, and scant cytoplasm. These cells can resemble immunoblasts and occasionally show lymphocyte-like features. Necrosis and mitotic figures vary across samples.

Immunophenotyping is crucial for diagnosing BPDCN because of its unique marker expression profile. The hallmark of BPDCN cells is the consistent expression of CD123 (IL-3 receptor alpha), CD4 and CD56, which form the diagnostic triad[22, 23]. BPDCN cells also express TCF4, a critical transcription factor, and additional markers like CD303 (BDCA2), TCL1, and CD2AP, increasing diagnostic specificity[4, 24]. BPDCN cells generally lack lineage-specific markers for B cells, T cells, myeloid cells, and natural killer cells, which is crucial for distinguishing BPDCN from other haematologic neoplasms such as acute myeloid leukaemia or T-cell lymphoblastic lymphoma[25, 26].

Molecularly, BPDCN is characterized by a complex array of cytogenetic abnormalities, including frequent deletions and mutations that disrupt cell cycles and impair apoptosis. Common mutations in TET2 and ASXL1, as well as abnormalities in the CDKN2A/CDKN2B locus, are observed in BPDCN[27-29]. Prevalent copy number variations, typically losses, impact genes critical for tumour suppression and the G1/S cell cycle transition[30-32]. Notable aberrations also occur in signalling pathways involved in epigenetic regulation and RNA splicing, with mutations in genes such as ZRSR2, SRSF2, and SF3B1. These splicing factor mutations underscore their role of these genes in BPDCN pathogenesis[33].

In a recent publication in the World Journal of Clinical Cases (Manuscript NO: 89230), Yi-Qian Ma *et al.* presented "Blastic Plasmacytoid Dendritic Cell Neoplasm: Two Case

Reports." This paper significantly advances our knowledge of BPDCN, focusing on its immunophenotypic and histopathological characteristics.

The study documents the immunophenotypic analysis of two patients, both of whom had samples that tested positive for CD4, CD56, and CD123. These markers are crucial for diagnosing BPDCN, distinguishing it from other haematologic malignancies and benign conditions. CD123 is particularly valuable, because it signals the plasmacytoid dendritic cell origin of the neoplasm and has both diagnostic and therapeutic implications. Histopathologically, BPDCN is characterized by a uniform infiltration of medium-sized blastic cells in the dermis and subcutaneous layers, notably sparing the epidermis. The researchers also noted a Grenz zone, a clear boundary between the tumor cells and epidermis, which is commonly observed in BPDCN.

These reports highlight the aggressive nature of BPDCN, as evidenced by rapid disease progression and a poor response to traditional chemotherapy in both cases. These observations underscore the urgency for early detection and the initiation of appropriate suitable treatments.

The findings of Yi-Qian Ma *et al.*'s findings enrich our understanding of BPDCN pathology, emphasizing the importance of accurate and timely diagnosis. The insights provided by these case studies are critical for guiding ongoing research and clinical strategies, aiming to improve patient outcomes in this challenging area of haematologic oncology. Readers are encouraged to review the full article to fully appreciate the detailed observations and their potential impact on patient care.

Pathological Insights and Clinical Relevance in BPDCN Management

In treating BPDCN, intensive chemotherapy regimens similar to those used for acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) are commonly used[34, 35]. These treatments can initially lead to remission, but the disease often relapses, making allogeneic haematopoietic stem cell transplantation (allo-HSCT) a vital consolidation therapy. allo-HSCT, which leverages the graft-versus-leukaemia effect for potentially curative outcomes[36], requires careful patient selection is required to

manage the associated high risks, especially in older patients or patients with comorbidities.

Pathologists are crucial in diagnosing BPDCN, selecting treatments, and monitoring the disease. Pathologist use of immunophenotyping and molecular analyses helps differentiate BPDCN from other haematologic malignancies. Through sequential biopsies and monitoring for minimal residual disease, pathologists assess treatment effectiveness, detect early signs of relapse, and provide essential data to help clinicians adjust treatment plans effectively.

Recent advancements have been made in targeted therapies that exploit the overexpression of CD123 on BPDCN cells. Tagraxofusp, a CD123-targeting antibody–drug conjugate, has shown promising results and has received approval for treating BPDCN[37]. Additionally, ongoing clinical trials are assessing IMGN632, another novel CD123-targeting drug, is being assessed for the treatment of both initial and relapsed/refractory cases of BPDCN in ongoing clinical trials[38]. By analysing the expression levels of CD123 and other markers, pathologists play a pivotal role in guiding therapy choices and optimizing patient outcomes as these new treatments are developed.

In their study, Yi-Qian Ma *et al.* explored the management of BPDCN, evaluating intensive chemotherapy regimens similar to those used for AML and ALL. Despite initial success in inducing remission, these treatments often result in high relapse rates, highlighting the aggressive nature of BPDCN. The authors highlight the crucial role of allo-HSCT in achieving potentially curative outcomes, stressing the need for careful selection of patients to reduce risks associated with treatment, especially in older individuals and those with comorbidities.

The paper also details the essential contributions of pathologists in managing BPDCN, from accurate diagnosis to ongoing patient monitoring. Immunophenotyping and molecular analysis enable pathologists to differentiate BPDCN from other haematologic malignancies, which is crucial for tailoring treatment strategies effectively and detecting early signs of relapse.

Furthermore, this study discusses innovative therapies such as Tagraxofusp, a CD123-targeting antibody– drug conjugate, as significant advancements in targeted treatment. By focusing on the overexpression of CD123 in BPDCN cells, these therapies represent a move towards personalized medicine, potentially revolutionizing patient care by aligning treatment with individual biomarker profiles.

The Future of BPDCN Management: Interdisciplinary Approaches

Effective management of BPDCN will increasingly rely on a collaborative approach that integrates pathology with clinical practice, improving both research and patient care. Advances in targeted therapies, including tagraxofusp and emerging treatments such as IMGN632, underscore the shift towards personalized medicine, which promises to revolutionize treatment for this rare cancer. Continuous research is essential to identify new therapeutic targets and refine current strategies.

Pathologists are central to these advancements, as their work in analysing complex pathological data and identifying key biomarkers is critical for selecting appropriate treatments for patients. Their expertise ensures that the insights gained from research are accurately applied in clinical settings, leading to more precise and effective treatment plans and improved outcomes for BPDCN patients.

CONCLUSION

BPDCN is a complex haematologic malignancy for which early detection and an in-depth understanding of its pathology are required for effective management. The treatment landscape for BPDCN is rapidly evolving with the introduction of targeted therapies such as tagraxofusp and the development of new agents such as IMGN632, marking significant progress towards personalized medicine. Pathologists play a crucial role in this progress, providing essential insights through sophisticated immunophenotyping and molecular analyses. These efforts not only increase diagnostic accuracy but also inform treatment decisions. Ongoing research and the collaborative efforts between pathologists and clinicians are vital for applying these scientific

developments in clinical settings, improving patient outcomes, and altering the prognosis of this challenging disease.

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