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Blast and Bursts: Unveiling Splenic Rupture in Blastic Plasmacytoid Dendritic Cell Neoplasia

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CASE REPORT

Blast and Bursts: Unveiling Splenic Rupture in Blastic Plasmacytoid Dendritic Cell Neoplasia

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Abstract

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare hematologic cancer, accounting for less than 1% of acute leukemias in the U.S. Diagnosis involves detecting markers like CD123, CD4, CD56, TCL1, and TCF4. Treatment typically involved acute leukemia therapies, but Tagraxofusp, a targeted therapy, was recently approved. Despite advancements, prognosis remains grim, with a median survival of around 1 year. Atraumatic splenic rupture (ASR) is a rare complication of this condition, with only five cases reported from 1994 to 2018. Here we present a case of BPDCN complicated by ASR.

This case emphasizes the challenges of diagnosing and treating BPDCN, noting its rarity and absence of standard therapy. Tagraxofusp has shown promising results but presents safety concerns like capillary leak syndrome, particularly in elderly patients with comorbidities.

Keywords: BPDCN, CD123, IL3Rα, Capillary leak syndrome, Tagraxofusp

1. Introduction

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) represents a rare hematologic malignancy, with incidence estimated to be less than 1% among all acute leukemias in the United States.[1,2] Common manifestations include skin lesions, cytopenias, lymphadenopathy and splenomegaly. Diagnosis involves demonstration of CD123, CD4, CD56, TCL1, and TCF4 on flow cytometry and/or immunohistochemistry. Historically, treatment has employed acute leukemia regimens, but a recent milestone occurred with the approval of Tagraxofusp, a CD123-directed cytotoxin. Despite therapeutic advancements, prognosis remains grim, with a median survival of approximately 1 year. A rare complication of BPDCN is atraumatic splenic rupture (ASR), with only five documented reports from 1994 to 2018.[3] Here we present a case of BPDCN complicated by spontaneous ASR.

2. Case presentation

An 84-year-old man with coronary artery disease, independent in his daily activities of living but being evaluated for exertional dyspnea, presented to the ER with two days of abdominal pain. His vital signs were normal, physical exam notable for chronic diffuse rash on his back. Lab tests showed elevated serum creatinine 1.5 mg/dL (previously 0.8 mg/dL), urate (12 mg/dL), white blood cell count 80,000 k/mcL with 53% blasts, total bilirubin 2.7 mg/dL (previously 1.5 mg/dL), hemoglobin 15 g/dL (previously 13.7 g/dL), and platelets 77 k/mcL.

Abdominal and pelvic computed tomography (CT) imaging revealed splenomegaly (17.2 cm). Due to suspected leukemia and risk of tumor lysis syndrome, the patient was treated with rasburicase, allopurinol, and IV fluids. Peripheral flow cytometry revealed a lymphocytic gate (18% of cells) containing B-cells with kappa light chain restriction (CD19+, CD20+, CD22+, CD5−, CD10−, CD11c−, CD103−, CD23−, CD200−) CD45 gate with (CD34−,

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CD117−, CD19−, CD20−, CD22−, CD10+, CD 33 equivocal, CD13−, HLA-DR+, CD4+, cMPO−, TdT−, cCD3−, cCD79a−). Initial differentials included marginal zone lymphoma, lymphoplasmacytic lymphoma, diffuse large B-cell lymphoma. A bone marrow biopsy and aspiration were performed with additional studies sent for cytogenetics and molecular testing.

The patient was admitted to the hospital and started on hydroxyurea for cytoreduction. His white blood count normalized, abdominal pain and renal injury resolved within 3 days, and was deemed stable for discharge with close outpatient follow up.

Less than 24 h post-discharge, the patient returned to the hospital with worsening abdominal pain. A repeat CT scan revealed splenic rupture with hemoperitoneum and was transferred to a tertiary care center and experienced cardiac arrest upon arrival. After approximately 10 min of cardiopulmonary resuscitation, spontaneous circulation was achieved. The patient was intubated and underwent an emergent exploratory laparotomy due to hemorrhagic shock from ASR. Multiple splenic lacerations with active bleeding were noted, and he underwent splenectomy resulting in hemodynamic stability. He remained stable and was extubated within 48 h without subsequent cardiac arrest events. The bone marrow biopsy resulted, showing blastoid infiltration and raising concerns for BPDCN as shown in Figs. 1 and 2.

The blastoid infiltrate was positive for CD 4, CD 10, CD 45, CD 123, TCL1A, CD33, BCL-2, and HLA-DR. Molecular studies revealed ASXL1, KRAS, TP53 and TET2 mutations, of which ASXL1 and TET2 are most common in myelodysplastic neoplasms. Splenic pathology revealed blastic infiltrates consistent with BPDCN, as seen in Fig. 3.

Tagraxofusp was considered for treatment but due to persistent hypoalbuminemia and the risk of capillary leak syndrome (CLS), therapy with venetoclax (VEN) was initiated instead, with azacitidine (AZA) added later. Considering BPDCN's propensity for central nervous system (CNS) involvement, empiric intrathecal therapy with methotrexate alternated with cytarabine was started. Following his extended hospital stay, his Eastern Cooperative Oncology Group (ECOG) performance status declined to 2. While initially tolerating treatment, he later developed cytopenias and weakness, leading to a dose reduction of VEN. Unfortunately, due to his age and comorbidities, he was not considered eligible for HSCT and will continue treatment with AZA/VEN.

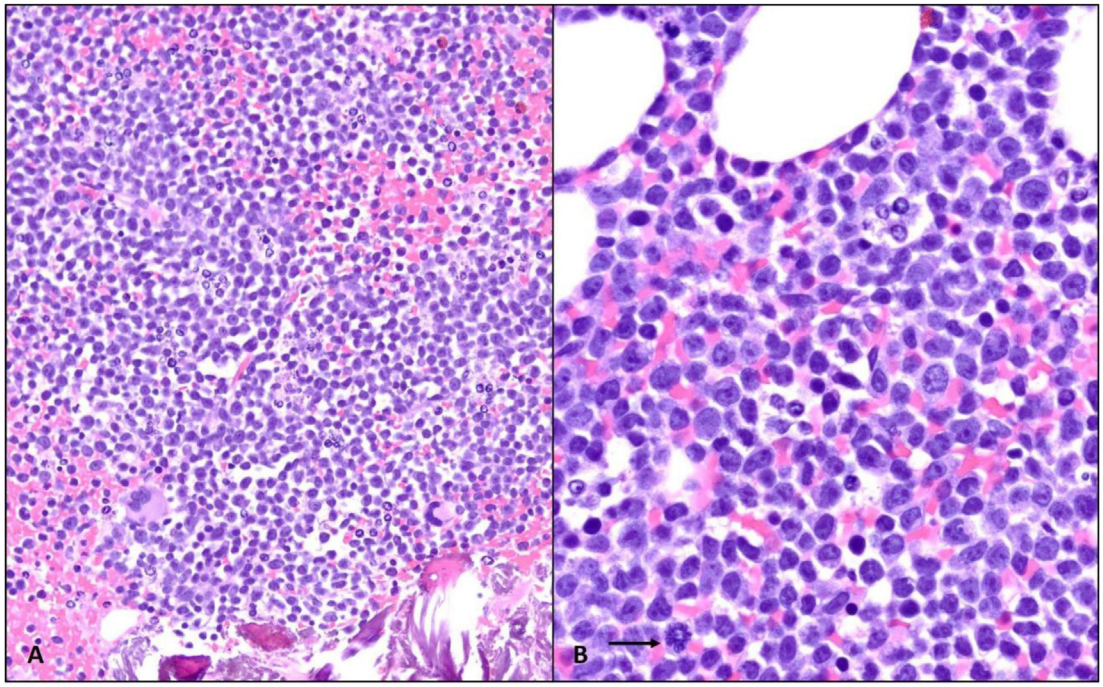

Fig. 1. Bone marrow clot section [Hematoxylin and Eosin (H&E) stain. A. Intermediate power view [200x magnification] of the clot section revealed extensive infiltration of atypical cells with medium-to-large blastoid mononuclear morphology in a background of scattered residual hematopoietic cells. B. High power view [400x magnification] of the clot section revealed a diffuse infiltrate of monotonous, atypical medium-to-large cells with scant-to-moderate cytoplasm, eccentric nuclei, slightly irregular nuclear contours, fine blastoid chromatin, one or more inconspicuous nucleoli and mitotic figure (arrow).

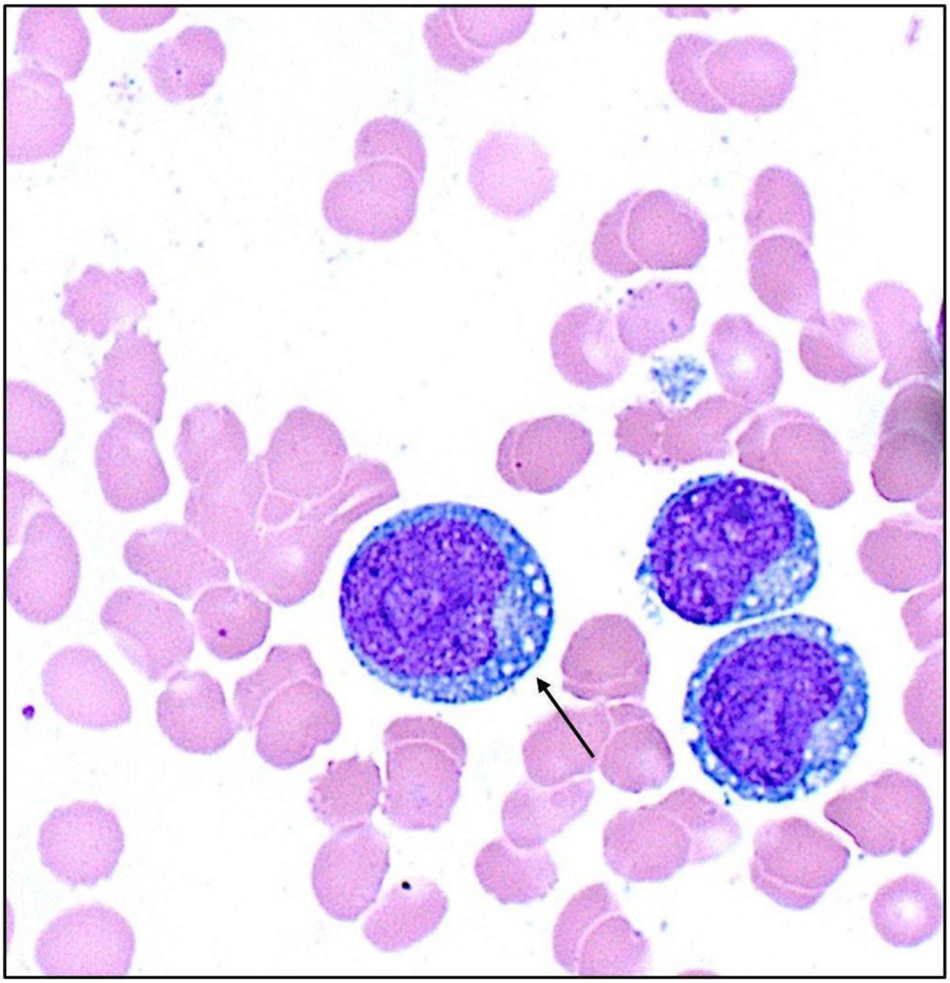

Fig. 2. Bone marrow aspirate [Wright-Giemsa Fuccillo stain modification]. [1000x magnification] Demonstrates involvement by atypical medium-to-large cells with basophilic, vacuolated cytoplasm, eccentric nuclei, irregular nuclear contours, fine chromatin and often small subtle nucleoli. The indicated cell (arrow) demonstrates the unique but not specific "string of pearls" peripheral arrangement of uniformly sized cytoplasmic vacuoles.

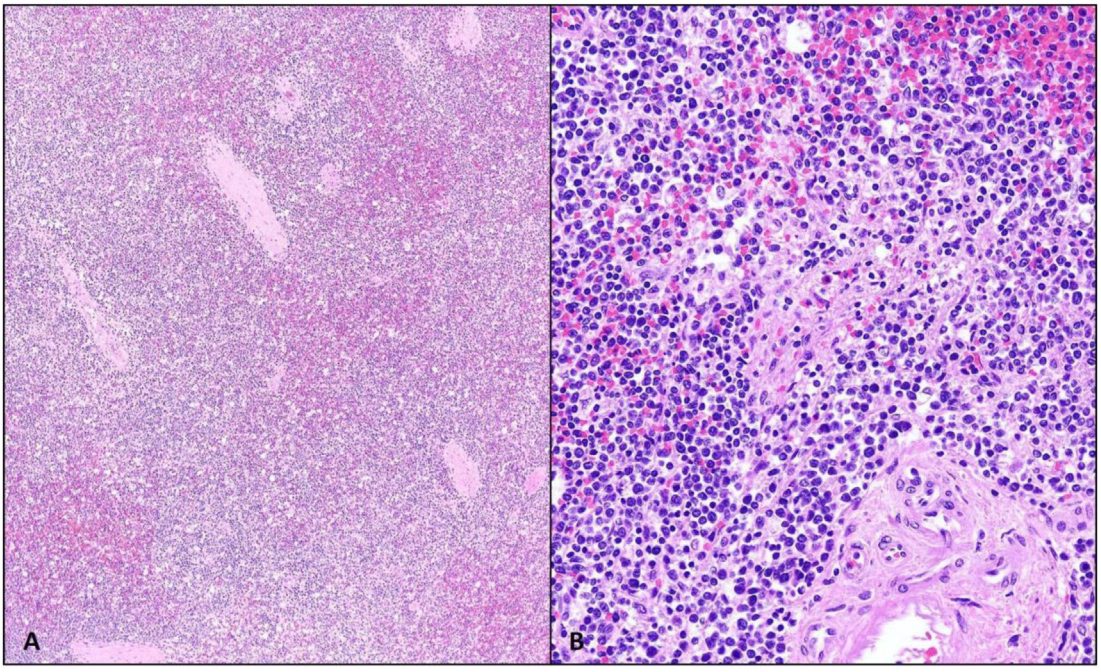

*Fig. 3. Spleen [H&E stain]. **A.** Low power view [40x magnification] demonstrates splenic tissue with expansion of white pulp by an abnormal infiltrate that extends irregularly into red pulp areas. **B.** Intermediate power view [200x magnification] reveals diffuse infiltration of white pulp by monotonous atypical medium-to-large cells with high nuclear to cytoplasmic ratio (N:C ratio) and slightly irregular nuclear contours.*

3. Discussion

BPDCN is a rare hematologic malignancy with a poor prognosis possibly due to factors like advanced age at diagnosis, rarity, and the absence of established standard therapies.

Plasmacytoid dendritic cells (pDCs) produce high levels of type 1 interferon (IFNs) during viral infections, and are pivotal in BPDCN.[4] The exact etiology of BPDCN remains unclear, postulated mechanisms include monoallelic and biallelic 12p13/ETV6 deletions,[5] secondary malignancy in the context of myelodysplasia,[6] and aberrant NF-kappa B activation along with alterations in TCF4.[7]

Clinical presentation varies, up to 90% of cases manifest with asymptomatic skin involvement.[8] While splenic infiltration is documented, ASR-associated BPDCN cases are rare, with only five ASR cases reported between 1994 and 2018.[9] Splenic infiltration by malignancy, coagulation disorders and severe splenomegaly may contribute to pathologic splenic ruptures.[3]

Microscopically, the cells appear as blasts with irregular nuclei, fine chromatin, agranular cytoplasm, resembling those seen in acute lymphoblastic leukemia (ALL). Diagnosis requires the expression of CD123 and another pDC marker (CD123, TCL1, TCF4, CD304, and CD303), in addition to CD4 and/or CD56, and the absence of certain markers.[8] This necessitates the expertise of an experienced pathologist for accurate identification.

Historically, BPDCN has been treated with chemotherapy regimens used for acute myeloid leukemia (AML) or ALL. Retrospective studies indicate that ALL-type regimens have slightly better response rates than AML-type regimens. Pagano El et al.'s study from 2005 to 2011 showed complete remission was achieved in 66% in the BPDNC patients treated with ALL-type regimen compared to 17% with the AML-type regimen.[8] CNS prophylaxis with intrathecal chemotherapy has been associated with improved overall survival.[10] Autologous and allogeneic stem cell transplantation have also been shown to improve overall survival. Survival rates at 4 years for patients who underwent auto-hematopoietic stem cell transplant (HSCT) and allo-HSCT were 82% and 53%, respectively, and progression-free survival rates were 73% and 48%, respectively.[11,12]

In 2018, Tagraxofusp was approved for managing BPDCN after showing remarkable clinical responses in a multicohort study involving 47 patients with previously untreated or relapsed BPDCN. The primary outcome, which was the combined rate of complete response and clinical complete response among previously untreated patients, was achieved in 72% of the 29 previously untreated patients, with an overall response rate of 90%. Survival rates at 18 and 24 months were 59% and 52%, respectively.[13]

Tagraxofusp targets CD123 (IL3Rα) with a fusion protein of IL-3 and a truncated diphtheria toxin, inhibiting tumor cell protein synthesis. However, 18% of patients experience CLS as a side effect.[13] A screening tool for CLS exists, assessing hypoalbuminemia, edema, hypotension, and cytokine release syndrome. The albumin cut-off is 3.2 g/dL based on the STML-401-0114 trial. If concern for CLS arises, management involves holding Tagraxofusp, administering high dose steroids and intravenous albumin.[14] The eligibility of elderly patients with chronic diseases for Tagraxofusp is uncertain. Our patient, with persistent albumin levels below 3.2 g/dl, was at risk for CLS, prompting us to choose alternative therapy over Tagraxofusp. One alternative treatment to Tagraxofusp is VEN, a selective BCL2 inhibitor, either alone or combined with chemotherapy. Case reports and retrospective studies indicate some success in BPDCN patients treated with VEN,[15–17] and is being studied in combination with Tagraxofusp to treat BPDCN.[18]

Clinicians should maintain a high suspicion for splenic ruptures, particularly in patients with hematological malignancies experiencing abdominal pain, despite its rarity. Anticipating splenic rupture can be difficult, as demonstrated in our case where symptom resolution occurred without significant intervention. An enlarged spleen on exam or imaging should alert the clinician to the possibility of impending ASR.

4. Conclusion

BPDCN is a rare malignancy with poor prognosis and no established guidelines for optimal treatment. Rarely, BPDCN can be associated with ASR. Traditionally, it has been treated with acute leukemia chemotherapy regimens. Recently however, novel therapies have been developed, such as Tagraxofusp that have shown promising results. These new therapies present unique safety concerns such as capillary leak syndrome which can limit who is eligible for these treatments, particularly in those with chronic medical comorbidities and advanced age. Further research is needed to determine optimal therapy in BPDCN, particularly patients who are at risk for adverse effects from Tagraxofusp.

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Conflict of interest

The authors have no conflict of interest, financial or otherwise.

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