

Blastic plasmacytoid dendritic cell neoplasm with skin, bone marrow involvement and transverse myelitis: a case report

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SUMMARY

Blastic plasmacytoid dendritic cell neoplasm is a highly aggressive myeloid neoplasm with a high rate of central nervous system recurrence. We present a case to illustrate central nervous system involvement and possible treatment options.

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INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare disease, which should be recognised by its characteristic immunophenotype (triple positive CD4+/CD56+/CD123+ phenotype without other lineage-specific markers). BPDCN is characterised by predominant cutaneous involvement with concomitant or ensuing spread to the bone marrow and peripheral blood. The clinical course is aggressive with a short overall survival irrespective of the initial presentation of the disease.

CASE DESCRIPTION

A 65-year-old man was hospitalised due to general malaise, abdominal pain and various cutaneous lesions. He was transferred to our centre because of pancytopenia. He had a prior history of colon adenocarcinoma with liver metastases treated with surgical resections and chemotherapy. He progressively developed multiple erythematous plaque skin lesions and had constitutional symptoms including night sweats and anorexia.

The physical examination revealed several demarcated erythematous non-indurated plaques in the lumbar region, splenomegaly, but no peripheral adenopathy's.

Laboratory results revealed cytopaenia with a microcytic anaemia, severe thrombocytopaenia, and lymphopaenia without neutropaenia. A consumptive coagulopathy (DIC) was present. Liver function abnormalities and strongly elevated LDH were noted.

Chest CT revealed a small zone of bronchiolitis paracardial in the left upper lobe, centimetric lymph nodes in mediastinum and hili. Abdominal CT revealed status after left hepatectomy and splenomegaly.

Histology of a lumbar skin revealed a monomorphic, epidermal-sparing diffuse infiltration of middle-sized cells with perivascular and focal localisation, some cells with blastic appearance, these cells co-expressed CD4, CD56, and CD123 and were negative for myeloperoxidase, CD30 and CD34. The proliferative index (Ki-67) was elevated in the basal cell layer.

Bone marrow histology showed a markedly hypercellular marrow (90%), with CD4+CD56+ small blast cells, negative for myeloperoxidase, T, B or NK cell lineage markers, and fibrosis grade 1. Bone marrow aspirate revealed 10% blasts with discrete dysplastic features in the myeloid and erythroid cell lines, suggesting MDS-EB2. Flow cytometry revealed a specific panel CD4dim/CD15+/CD56+/CD34-/

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Keywords: blastic plasmacytoid dendritic cell neoplasm (BPDCN), stem cell transplantation (SCT).

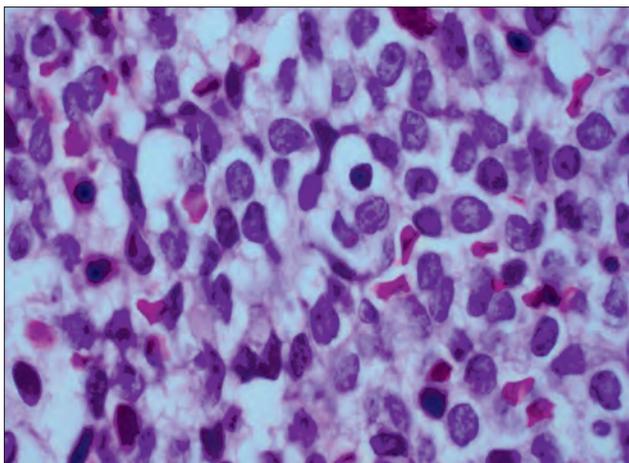


FIGURE 1. The bone marrow trephine shows a dense blast cell infiltrate. The blasts have nuclei with a fine chromatin pattern that contain a nucleolus.

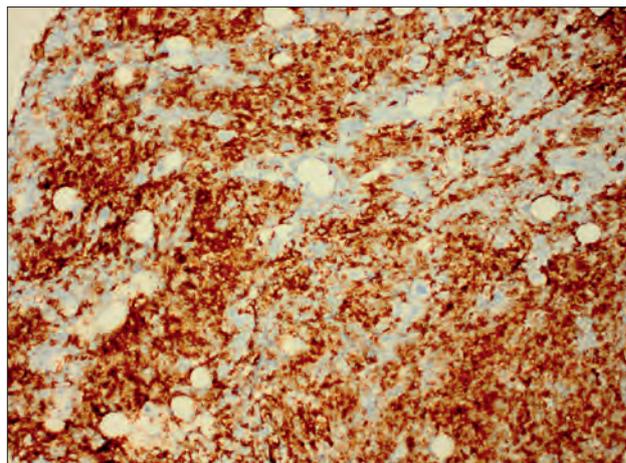


FIGURE 2. The blasts in the bone marrow stain strongly for CD 56.

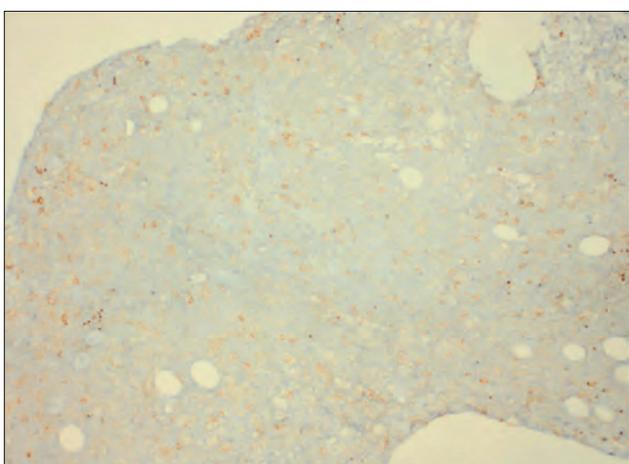


FIGURE 3. Cutaneous biopsy showing an infiltrate that consists of blasts and smaller reactive (mainly T-) lymphocytes.

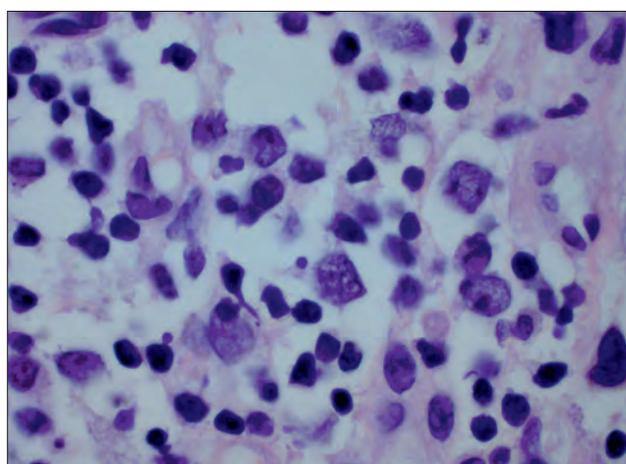


FIGURE 4. The blasts in the dermal infiltrate are positive for CD56.

CD117+/+/CD123+/CD7+/+/CD38+/HLA-DR+/CD-45dim. NGS analysis showed a SRSF2 hotspot mutation and a deletion in ASXL1. Cytogenetics showed an aberrant karyotype with del(20q).

Based on these clinical, microscopic, immunophenotypic, histologic and genetic features a diagnosis of BPDCN with cutaneous and bone marrow involvement was established.

The patient was treated with a classical AML induction therapy consisting of cytarabine and idarubicin (7+3), complicated by probable invasive pulmonary aspergillosis which was treated with voriconazole. He reached a complete remission based on negative bone marrow aspirate and skin biopsy. A diagnostic lumbar puncture was normal. He then received a second AML induction chemotherapy consisting of idarubicin and high dose cytarabine (3+3).

Shortly after starting the second chemotherapy he developed

fever and rapidly progressive rising motor and sensory impairment of the lower limbs and sphincter impairment. Clinical and radiological findings were compatible with acute transverse myelitis in the region of D2 to D10. An extensive search for microbiological or leukemic aetiology including a lumbar puncture remained negative. During aplasia, there was a temporary resolution of the symptoms, with re-appearance after haematological recovery. Finally a new lumbar puncture revealed tumour cells with the initial phenotype compatible with CNS involvement. At that time, the general condition of the patient was rapidly deteriorating, and comfort therapy was started. He succumbed to his disease a few days later.

DISCUSSION

BPDCN is a rare aggressive, hematologic malignancy derived

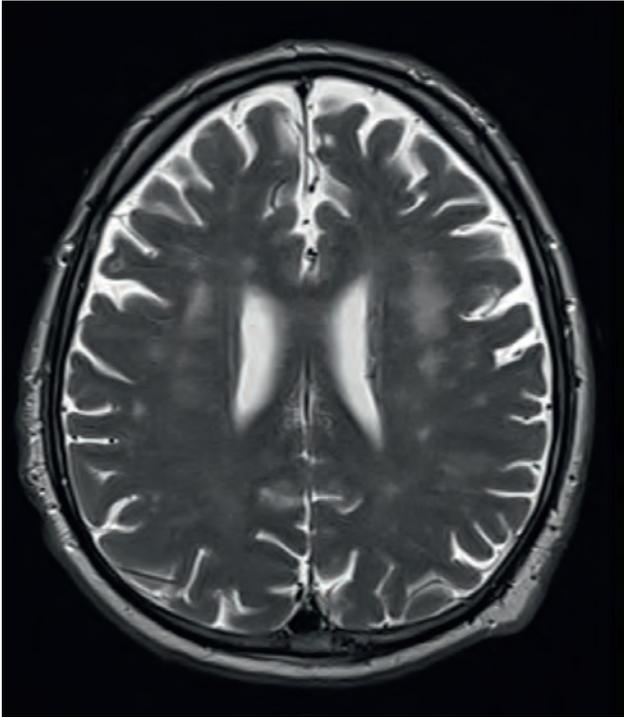


FIGURE 5. An MRI scan of the brain shows multiple T2 / FLAIR diffuse hyperintense lesions.

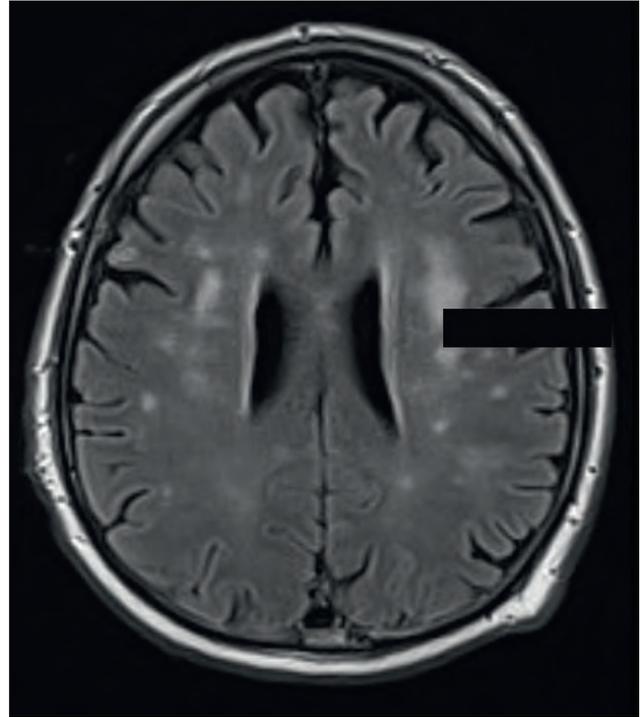


FIGURE 6. An MRI scan of the brain shows multiple T2 / FLAIR diffuse hyperintense lesions.

from the precursors of plasmacytoid dendritic cells with a high frequency of cutaneous and bone marrow involvement and leukemic dissemination. The tumour cells express CD4, CD56 and the plasmacytoid dendritic cell associated antigen CD123 (IL3 alpha chain receptor). Since 2008, it is recognised by the WHO as a distinct entity and separately listed in the group of ‘acute myeloid leukaemia’s and related precursor neoplasms’.

An accurate diagnosis of BPDCN is essential in order to provide treatment promptly, considering that the initial clinical presentation is often indolent. BPDCN can overlap with other hematologic neoplasms. The triple positive CD4+ CD56+ CD123+ phenotype associated with negativity for lineage-associated antigens is considered a unique phenotype pathognomonic of BPDCN.

Ten to twenty percent of cases of BPDCN are associated with or develop into other myeloid neoplasms such as CMML, MDS and AML. In this case there was an association with MDS-EB2 with 10% marrow blasts, erythroid and myeloid dysplasia, cytogenetic (del(20q)) and molecular findings (SRSF2 and ASXL1 mutations). ASXL1 mutations are frequently identified in patients with BPDCN (~30%) and a combination with SRSF2 has been described.¹ BPDCN shows a high rate of central nervous system (CNS) recurrence (~30%) and requires routine screening for CNS involvement at diagnosis, treatment and/or prophylaxis.²

AVAILABLE TREATMENT OPTIONS

Because of the rarity of BPDCN, there is no apparent consensus for the treatment of BPDCN and are few prospective trials. Intensive therapy for acute leukaemia both AML as well as ALL-like increase the rate of complete remission, and allogeneic or autologous HSCT within the first remission appear to provide some survival benefit.

Several regimens have been used to treat these patients including AML-like therapy, ALL-like therapy, CHOP-like and NK/T-cell like therapy (based on high-dose methotrexate, L-asparaginase, +/- dexamethasone) as well as haematopoietic stem cell transplantation (SCT).

A retrospective analysis of the first line treatments used in France between 2000 and 2013 for 86 patients recruited in the French network of BPDCN showed trend to superiority of ALL-, AML- and NK/T-like therapies compared to CHOP-like and other groups, in terms of response rates, relapse rates and remission duration.³

A retrospective Italian study showed superiority of an ALL-type regimen in terms of both response and overall survival (OS). Patients treated with an AML-type regimen had an OS of 7.1 months versus 12.3 months for those receiving an ALL-type regimen ($p=0.02$).⁴

A retrospective Japanese study compared the outcomes of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (autologous SCT) and allo-



FIGURE 7. A photograph of demarcated erythematous non-indurated skin plaques.

genic hematopoietic stem cell transplantation (allogeneic SCT) in 25 BPDCN patients (allogeneic SCT fourteen patients, auto-HSCT eleven patients).⁵ After a median follow-up of 53.5 months, the OS rates at four years for patients who underwent autologous SCT and allogeneic SCT were 82% and 53% ($p=0.11$), respectively, and progression-free survival rates were 73% and 48% ($p=0.14$), respectively. Autologous SCT for BPDCN in CR1 appears to provide promising results and deserves further evaluation in the setting of prospective trials. A prospective trial of AspaMetDex protocol, consisting of intravenous L-asparaginase, high-dose methotrexate and oral dexamethasone has been conducted in seven patients in France and prolonged survival and induced complete remissions. After three cycles of treatment, 5/7 patients had responded (71%) with 4/7 having CR (57%). Median OS was 12.1 months (range, 2-47) and the median RFS was ten months (range, 2-47).⁶

A prospective study evaluated the impact of intrathecal (IT) prophylaxis and treatment in thirteen cases of BPDCN at diagnosis ($n=10$) and relapse ($n=3$) and compared the results on patient outcome to a retrospective cohort of 23 BPDCN patients. Despite absence of neurological symptoms at disease staging, occult CNS involvement was detected in 6/10 cases at diagnosis and 3/3 cases at relapse. IT prophylaxis and treatment seemed to improve OS and CNS recurrence-free survival, confirmed in a univariate analysis of retrospective BPDCN cohort. These results suggested that CNS could be a tumour cell sanctuary in BPDCN patients with leukemic presentation due to a limited crossing of blood-brain barrier by cytostatic agents.²

An ongoing phase II single-arm, open-label, clinical trial of a front-line single therapy with SL-401 in 32 adult BPDCN patients (nineteen untreated, thirteen relapsed/refractory)

demonstrated a single agent activity including multiple CRs.⁷ SL-401 is a recombinant fusion protein directed to IL3 alpha receptor (CD123). Overall response rate was 84% (27/32) of which 95% (18/19) in first-line and 69% (9/13) in relapse/refractory setting. Complete response rate was 59% (19/32) including 88% (14/16) in first-line and 31% (4/13) in relapsed/refractory patients. Twenty five percent (8/32) of patients who achieved a remission on SL-401 were subsequently bridged to SCT including one relapsed/refractory patient. In first-line BPDCN patients treated at 12 $\mu\text{g}/\text{kg}/\text{day}$ ($n=16$), the median OS has not been reached. Its frequent side effects were hypoalbuminemia (43%), transaminitis (43%), and thrombocytopenia (26%). One patient had capillary leak syndrome grade 5 (3.1%).

Finally, bortezomib targeting the nuclear factor-kappa B pathway is considered a promising therapeutic approach. Bortezomib efficiently inhibits nuclear factor-kappa B pathway in BPDCN cells from patients *in vitro* and *in vivo* in a mouse model.⁸

CONCLUSIONS

BPDCN is a very rare and highly aggressive hematologic malignancy derived from plasmacytoid dendritic cells. It has a high frequency of cutaneous and bone marrow involvement, leukemic dissemination and CNS involvement. It has distinct immunophenotypic features (CD4+/CD56+/CD123+). BPDCN has a poor prognosis with a median overall survival of twelve months from diagnosis. Most cases (80-90%) show an initial response to multi-agent chemotherapy but relapses with resistance to drugs are regular.

There is no apparent consensus on the treatment and AML as well as ALL-like therapies have been used. Allogeneic or autologous SCT appear to provide some survival benefit. Occult CNS disease should be actively screened for at diagnosis and intrathecal prophylaxis and treatment can improve outcomes. Novel agents are being tested such SL-401 (a targeted therapy directed to the interleukin-3 receptor (IL-3R α ; CD123)) show promising results.

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KEY MESSAGES FOR CLINICAL PRACTICE

- 1** Highly aggressive hematologic malignancy with cutaneous manifestations; derived from plasmacytoid dendritic cells (pDCs).
- 2** Diagnostic criteria: CD4, CD56, CD123 and other pDC markers.
- 3** Occult CNS disease is frequent and intrathecal prophylaxis and treatment should be considered.
- 4** AML as well as ALL-like therapies have been used and allogeneic or autologous HSCT appear to provide survival benefit.
- 5** Novel targeted therapies (SL-401) induce high overall response and complete response rates.

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