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Case Report

A Child with Blastic Plasmacytoid Dentritic Cell Neoplasm Complicated with Perianal Necrotising Fasciitis

WYK ***Chan***, RYY ***Leung***, AKS ***Chiang***, DKL ***Cheuk***

Abstract Blastic plasmacytoid dendritic cell neoplasm is an uncommon aggressive haemato-lymphoid neoplasm derived from type 2 dendritic cells which occur mainly in adults and elderly. It usually manifests as cutaneous lesions on face, scalp, trunk or limbs. In this report, we describe a 6-year old girl with unusual presentation of septic shock and perianal necrotising fasciitis, warranting urgent laparotomy, colectomy, perineal debridement and long term colostomy. She achieved complete remission with acute lymphoblastic leukaemia-based chemotherapy protocol.

Key words Blastic plasmacytoid dendritic cell neoplasm; Necrotising fasciitis; Perianal

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an uncommon aggressive haematological neoplasm derived from type 2 dendritic cells (DC) and it occurs much more commonly in adults and elderly.[1] It usually manifests as cutaneous lesions over face, scalp, trunk or limbs. To the best of our knowledge, less than 50 paediatric cases have been reported worldwide.[1] Here we describe a 6-year old girl with unusual clinical presentation of septic shock and perianal necrotising fasciitis for this rare disease.

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Case Report

A 6-year-old girl developed acute onset of high fever, watery diarrhoea, vomiting and abdominal pain. Diarrhoea worsened over the next 2 days with mucus and fresh blood noted on tissue paper upon wiping and pain on defaecation. Progressive redness and swelling of buttock were noted and the child was brought to hospital 3 days after symptom onset. Appetite remained well all along and no weight loss was noticed.

The child was in septic shock upon admission requiring fluid resuscitation. Significant buttock swelling with hyperpigmentation was seen (Figure 1). Intravenous clindamycin and metronidazole were given empirically. Examination was unremarkable otherwise. No lymphadenopathy or hepatosplenomegaly were noted. Complete blood picture showed cytopenia with left-shift of white blood cells and toxic granulations, compatible with severe sepsis. Haemoglobin level was 8.4 g/dL, platelet count 142 x 10^9/L, and white cell count 0.2 x 10^9/L. C-reactive protein was elevated to 353 mg/L. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were prolonged but no disseminated intravascular coagulopathy (DIC) was noted (PT 15.6s, APTT 40.4s, INR 1.4, fibrinogen 8.3 g/L, D-dimer 0.4 mg/ml). Electrolytes, renal and liver function tests were unremarkable. Abdominal X-ray showed dilated

small and large bowel loops but no fluid levels or free intraperitoneal gas was demonstrated. Computed tomography of the abdomen revealed severe mucosal swelling at rectum and sigmoid colon. Severe colitis with abscess formation and perforation were suspected. Emergency laparotomy, colectomy, colostomy and perineal debridement were performed subsequently. Biopsy of skin and subcutaneous tissue revealed no conclusive diagnosis on histological examination due to extensive necrosis. Subcutaneous fatty tissue and perineal wound swabs together with blood culture later grew Group G streptococcus. Fever and skin erythema gradually subsided post-operatively with antibiotics. Complete blood count and clotting profile subsequently normalised except persistent lymphopenia (WCC $8.1x10^9$/L, ALC $0.2\text{-}0.5x10^9$/L, Hb 12.3 g/dL, platelet $427x10^9$/L, PT 11.7, INR 1.1, APTT 33.1) when sepsis resolved and transfusions given. Immunology team was consulted for persistent lymphopenia with dihydrorhodamine test (DHR) test and lymphocyte subsets performed. Bone marrow examination was performed and showed predominance of immature mononuclear cells (93%). Flow cytometry of marrow blood showed that the cells were positive for CD4, CD56, CD7, CD123, CD117 and HLA-DR while negative for myeloid markers (CD13, CD33 & myeloperoxidase) and B- & T-lineage markers. Tdt-positivity is revealed on trephine biopsy sections. Peripheral blood smear revealed occasional (8%) abnormal mononuclear cells presumed to be blasts (Figure 2, blast cell on the right with lymphocyte on the left side as comparison). In-situ hybridization (ISH) for Epstein-Barr virus (EBV) encoded ribonucleic acid (RNA) [EBER] was negative. Cerebrospinal fluid (CSF) showed no malignant cells. Diagnosis of BPDCN was made.

She was started on chemotherapy according to our contemporary Children's Cancer and Leukaemia Group (CCLG) 2008 intermediate risk protocol for acute lymphoblastic leukaemia (ALL). Induction chemotherapy consisted of 7 days of prednisolone prophase and 4 weeks of standard 4-drug regimen (dexamethasone, vincristine, daunorubicin, and asparaginase). Intrathecal chemotherapy was also incorporated in the protocol. Bone marrow reassessment on Day 15 of chemotherapy showed regenerating marrow with no abnormal infiltrate. She continued early intensification, consolidation, delayed intensification and maintenance chemotherapy without significant complications. The whole treatment lasted for 2 years and she remained well now off treatment for more than 2 years. End of treatment bone marrow examination showed complete remission of disease. Latest magnetic resonance imaging of abdomen showed distorted anatomy of anal canal. The anal sphincters were destroyed as both internal and external sphincters were not demarcated. She may need permanent colostomy.

Discussion

BPDCN is an uncommon aggressive haematolymphoid malignancy derived from plasmacytoid (type 2) DC.

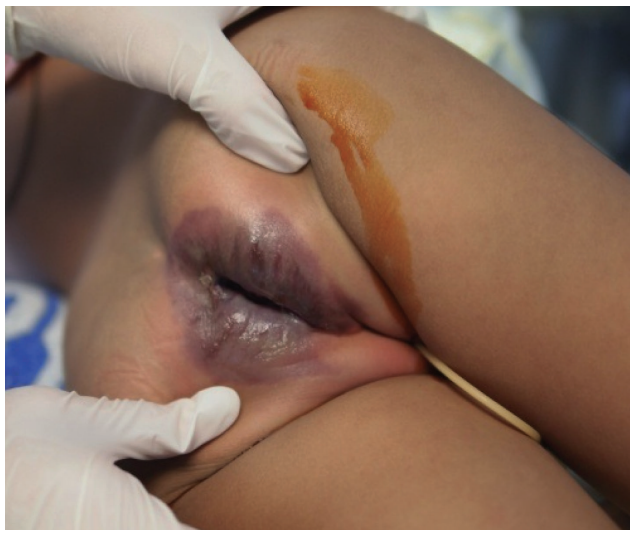

Figure 1 Violaceous skin pigmentation demonstrating necrotising fasciitis of buttock.

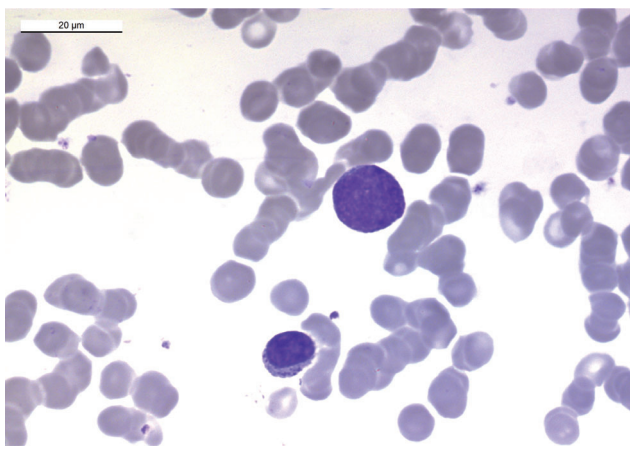

Figure 2 Photomicrograph of blastic plasmacytoid dendritic cell with small vaculoles riming scanty cytoplasm.

Nomenclature for this disease entity has been evolved over past two decades with increased understanding on underlying biology. It was initially described as acute agranular CD4+ natural killer (NK) cell leukaemia in 1994 by Adachi et al.[2] (due to its unique agranular morphology and phenotype $CD4^+CD56^+CD15^+CD3^-$), later coined as blastic NK cell lymphoma (due to its blastic appearance and CD56 expression)[3] and agranular $CD4^+CD56^+$ haematodermic neoplasm/tumour[4] (based on its immunophenotype and skin predilection). Current nomenclature was employed in the 2008 WHO classification of tumours of the haematopoietic and lymphoid tissues and classified as a distinct entity under the group of acute myeloid leukaemia (AML) and related precursor neoplasms. It accounts for 0.7% of primary cutaneous skin lymphomas[5] and occurs much more commonly in adults and elderly (median age at diagnosis is 65-67 years) with modest male predominance (male-to-female ratio is 2.5:1).

Around one-third of the patients with BPDCN present as cutaneous lesion only[6] of variable size (few millimetres to 10 centimetres), shape (localised or diffuse, nodular or patchy) and colour (erythema, hyperpigmentation, purpura or ulceration).[1] Most common areas of involvement include face or scalp (20%), lower limb (11%), trunk (9%), upper limb (7%) and mucosa. As for our patient, septic shock and perianal necrotising fasciitis are unusual clinical presentations of this rare disease. Bone marrow involvement and leukaemic dissemination may occur as in this girl with 85% blasts in marrow and 8% in peripheral blood. Cytopenia (thrombocytopenia 78%, anaemia 65%, neutropenia 34%, and hyperleucocytosis infrequent) is another disease feature which is demonstrated in this patient (mainly anaemia and neutropenia, no significant thrombocytopenia). In addition, lymphadenopathy and splenomegaly are common though not seen in our patient. Other clinical manifestations include hepatomegaly or involvement of other organ systems such as tonsils, paranasal cavities, lungs, eyes, central nervous system (CNS), and paravertebral region. Worth noting is that a minority of BPDCN patients would present as leukaemia without skin involvement and thus a bone marrow examination is warranted.

Diagnosis is usually based on skin biopsy and good quality specimen is essential for diagnosis. Morphologically it appears as an infiltrate of monomorphic, medium-sized, poorly differentiated cells extending to subcutaneous fat while sparing the epidermis. Unfortunately, only necrotic tissues were obtained from surgical debridement of the affected areas in our patient and diagnosis was not reached at the time of surgery.

Immunophenotyping is crucial in confirming the diagnosis and filtering out other differential diagnoses of haematological malignancies with cutaneous manifestations, such as $CD56^+$ AML or myeloid sarcoma, nasal-type extranodal NK/T cell lymphoma, subcutaneous panniculitis-like T cell lymphoma (SPTCL) and cutaneous T cell lymphoma (CTCL). Garanche-Ottou et al[7] proposed immunophenotypic diagnosis of BPDCN including coexpression of CD4 and CD56/NCAM, positivity of plasmacytoid dendritic cell specific antigens (CD123/IL3RA, BDCA-2/CD303/CLEC4E and/or BDCA-4) and negativity of other T-lineage (CD3), monocytic (CD11c), myeloid (MPO) and B-lineage (CD79a) markers. Positivity of CD43/SPN, CD45RA and other DC2 markers (TCL1/TCL1A, SPIB/CTLA1/GZMB) also support the diagnosis. A significant proportion of cases are also positive for CD68, CD33, CD7 and Tdt. In our patient, diagnosis of BPDCN was made when flow cytometry demonstrated positivity towards CD4, CD56 and CD 123, while negative for myeloid and B-cell markers.

Optimal treatment is still unknown due to paucity of data and absence of prospective clinical trials. Heterogeneous treatment protocols were employed depending on institutional preferences. Small retrospective analyses suggest that younger patients with solely cutaneous disease with more immature cells histologically have better response to therapy and higher complete remission rates using ALL-like induction therapy[8] as in our patient. Allogeneic haematopoietic stem cell transplantation (HSCT) after first complete remission (CR) is recommended in adults due to high relapse rate, but reserved as second line for children after second CR on relapse. Pagano et al has recently published a diagnostic and treatment algorithm for BPDCN.[9] Novel treatment modalities mainly targeted therapeutic agents under active research have also been mentioned recently by Falcone et al,[10] such as hypomethylating agent 5-azacytidine (5-Aza), CD123 / IL3 receptor alpha (IL3Rα) inhibitor SL401, fusion toxin DT388IL3 containing diphtheria toxin (DT388) linked to interleukin-3 (IL3), NF-κB pathway inhibitors Bortezomib and BMS-345541, phosphoinositide 3-kinase (PI3K) / protein kinase B (AKT) pathway inhibitor MK-2206, bromodomian and extraterminal (BET) domain protein inhibitor as well as monoclonal antibodies

epratuzumab, gemtuzumab ozogamicin and lorvotuzumab mertansine (LM/IMGN901/BB-10901).

To conclude, BPDCN is a rare aggressive haematological neoplasm which commonly presents with cutaneous lesions. High index of clinical suspicion may facilitate early diagnosis and treatment. Accurate diagnosis hinges on immunophenotyping by flow cytometry on bone marrow samples and histopathology of good quality skin biopsy. Treatment with ALL-like chemotherapy seems promising in achieving complete remission. The role of HSCT and targeted therapy remain to be defined.

Declaration of Interest

All the authors report no conflicts of interest.

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