Blastic plasmacytoid dendritic cell neoplasm in an elderly woman

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SUMMARY

Blastic plasmacytoid dendritic cell neoplasm (a.k.a. NK cell lymphoma, CD4+CD56+ haematodermic neoplasm) is a rare aggressive tumour that arises from plasmacytoid dendritic cell precursors. We report the first case from Malaysia of a 79-year-old Chinese woman who presented with purpuric plaques and nodules produced by pleomorphic CD4+, CD56+, CD68+, CD123+ and CD303+, but CD2AP- mononuclear cell infiltrates. Leukemic dissemination occurred and she succumbed to disease without treatment 4 weeks after diagnosis and 9 months after onset of cutaneous disease.

KEY WORDS:
Blastic plasmacytoid dendritic cell neoplasm; NK cell lymphoma; CD4+CD56+ haematodermic neoplasm; precursors'

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare form of aggressive tumour developed from the precursors of plasmacytoid dendritic cells. This condition was previously termed blastic NK cell lymphoma or CD4+CD56+ haematodermic neoplasm (CD4/CD56 HN) [1]. It has a high risk of developing cutaneous, lymph node and bone marrow involvement, and leukemic dissemination. To our knowledge this is the first reported case of BPDCN in Malaysia.

CASE REPORT

A 79-year-old Chinese woman presented with an 8-month history of mildly pruritic nodules and plaques on the face and trunk. It started on the back and subsequently involved the nose and cheek. It was occasionally pruritic. There was no fever. Her past medical history included hypertension and ischaemic heart disease for which she was receiving propanolol, verapamil and isosorbide nitrate. Hydrochlorothiazide was withheld since the nodules were noted. She was a retired dulang washer, a mother of 9 children and lived in Cameron Highlands, Malaysia

Examination of the skin showed multiple purpuric nodules and plaques of varying sizes, ranging from 3 to 4 cm on the nose, right cheek, forehead, right upper back and pre-sacral areas. See Figure 1. There was no hepatosplenomegaly or lymphadenopathy. Preliminary investigations showed Hb 15.2 g/l, TWBC 9600 (N53%, L33%, M8%, E5%, B1%), Platelets 153 000 , ESR 2 mm/hr. A full blood picture was not performed. Human immunodeficiency virus antibodies was negative. Ultrasound scan of the abdomen was normal. A skin biopsy from one of the purpuric nodules was done and it showed dense pandermal infiltrates of medium to large mononuclear cells with pleomorphic cleaved nuclei. See Figure 2. The epidermis was atrophied with a clear subepidermal zone. Based on the morphology, the differential diagnosis were cutaneous T cell lymphoma or leukemia cutis. Initial immunohistochemical studies was performed at the University of Malaya Medical Centre in Kuala Lumpur. It showed that the neoplastic cells were strongly immunoreactive for LCA (leukocyte common antigen) and CD43. A few cells showed positivity for Tdt (terminal deoxynucleotidyl transferase). They were negative for CD3, CD20, CD57, CD30 and ALK-1 protein. Based on the immunohistochemical findings, the diagnosis was still inconclusive. Further confirmatory immunohistochemical srudies was required for definite diagnosis. As the stains were not available in Malaysia, paraffin blocks were sent to Dijon (France) for a more exhaustive immunohistochemical study.. The neoplastic cells were CD123+ and CD303P (most specific PDC markers).They were also immunoreactive for CD4, CD56, CD 68 and CD 303. CD3 and CD2AP were negative (CD2AP was provided by Dr Marafioti, Oxford). These results confirmed the diagnosis of BPDCN. See Figure 2. The patient developed severe hypotension three weeks after her first presentation. Her blood investigations showed Hb 6.7gm%, TWBC 7300 (N42%, L10%,M47%, with blasts cells and few myelocytes) and platelets 14 000. The blood film was reported as being suspicious for monocytic leukemia. Her LDH was 2981 U/l. She was transfused with packed cells and platelet concentrates. After discussion with her haematologist, the family decided against chemotherapy and opted for palliative care. No further examinations were performed such as bone marrow biopsy, or CT scan. She passed away a week later.

DISCUSSION

Plasmacytoid dendritic cell (PDC) is a Th2-type dendritic cell precursor. It is an important effector cell characterized by its capacities to produce large amount of alpha interferon and to differentiate into dendritic cell. They circulate in the blood as veiled cells and enter the lymph node and mucosal site in response to immune stimulation. PDCs are scarce under normal conditions.

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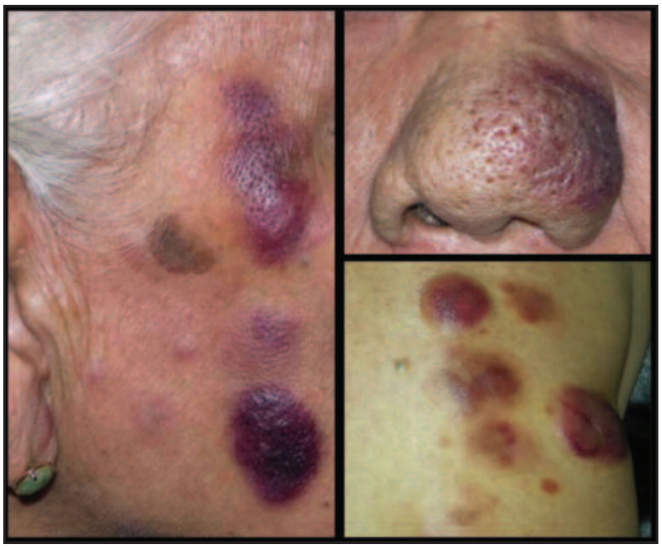

Fig. 1 : Multiple purpuric patches, nodules and plaques on the nose, right side of the face and right upper back.

Table I: Table showing the immunophenotypes of BPDCN, AML and T/NK type nasal

	BPDCN	AMLs	T/NK type nasal
CD4	+	+/-	-
CD56	+	+/-	+
CD43	+	-	+
CD303	+	-	-
CD123	+	-	-
TCL1	+	-	-
CLA	+	+	+/-
MPO	-	+/-	-
CD68	+/-	+/-	-
TiA1/GranzB	-	-	+
EBER	-	-	+
CD2	+/-	-	+/-
CD7	+/-	+	+/-
CD3	-	-	+/-

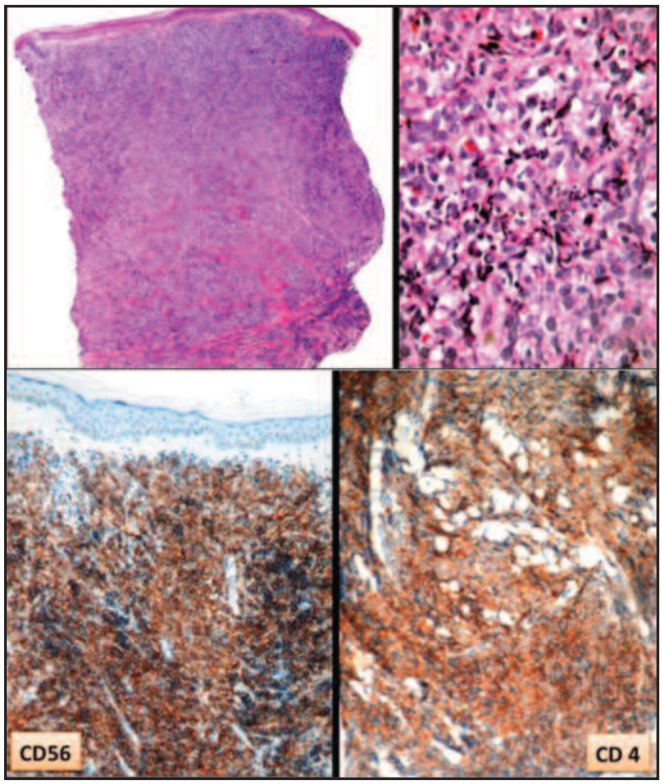

Fig. 2 : Biopsy of the skin showed the entire dermis had dense infiltrate of medium to large mononuclear cells with pleomorphic cleaved nuclei. The epidermis was atrophied with a clear subepidermal zone. Immunohistochemistry studies showing a positive CD4 (clone NCL-CD4-368 1/20) and CD56 (clone NCL-CD56-1B6 1/50).

Blastic plasmacytoid dendritic cell neoplasm is a rare and recently classified as a disease derived from PDC. In the WHO-EORTC classification of lymphoma, blastic natural killer cell has been replaced with CD4+/CD56+ HN because of its derivation from a plasmacytoid dendritic cell precursor [1]. Plasmacytoid dendritic cells were first identified by Lennert et al in human lymph nodes more than 50 years ago. The plasmacytoid dendritic cells belong to a population of cells that is typically found in cell clusters in T-cell rich interfollicular areas of peripheral lymphoid tissue. These cells contain rich amount of rough endoplasmic reticulum whose major proteins comprise of type I interferon. In 1999, Petrella et al reported the first large series of 7 patients with agranular CD4+CD56+ haematodermic neoplasm. They found that this tumour was characterised by skin tropism.. The tumours were confined to the skin and regional lymph nodes and can spread to the bone marrow without hepatosplenic involvement.

Subsequently Petrella et al reported an additional 7 cases in 2002 of CD4+ CD56+ HN and presented a rare population of cells that appeared to be related to plasmacytoid monocytes because they also expressed CD68 and some bright levels of CD123 [2]. Blastic plasmacytoid dendritic cell neoplasm is a rare disease and has been sporadically reported in United States and China as well.

Diffuse expression of CD43, LCA/CD45 with absence of CD20 and CD30 usually implicates leukaemia cutis or blastic plasmacytoid cell neoplasm (CD4+CD56+ hematodermic). Regional CD3 staining could represent tumour infiltrating lymphocytes or T-cell lymphoma. Additional immunohistochemistry tests including CD4, CD56, CD68 and myeloperoxidase allows more accurate classification of this neoplastic process.

In a CD3- and CD20- skin lesion, one needs to suspect localisation of a myelomonocytic proliferation or a plasmacytoid dendritic cell neoplasm (PDC neoplasm). For CD4+ and CD56+cases, further specific stains such as CD303, CD123, CD2AP and less specific stains such as TCL1 and

BCL11a are needed to confirm a PDC neoplasm. It is also important to look for peripheral monocytosis as it could be the first clinical manifestations of chronic myelomonocytic leukemia (CMML). It is interesting to note that CD2AP is negative in this patient though most cases (95%) are usually positive.. CD2AP is located on chromosome 6p12.3. Chromosome 6 is frequently affected by losses in BPDCN. Del(6q) is a recurring abnormality but sometimes one can see deletion on p arm. Cota et al reported cutaneous lesions of BPDCN showed a greater variability of morphologic and phenotypic features. For instance, negativity of 1 among these 4 markers, CD4, CD56, CD123, and TCL-1, was seen in 11 of 45 biopsies (24%) [3].

High levels of CD123+ expression can be used to distinguish CD4+CD56+ HN from non Hodgkin lymphoma but may not be sufficient to rule out myelomonocytic leukemia. The presence of CD123, CD4 and CD56 together with CD13, CD14, CD15, CD33 and MPO negativity can distinguish it from myelomonocytic leukemia.

Fontaine et al reported a case affecting the left cheek that was treated aggressively with methotrexate–asparaginase and local radiotherapy and was in complete clinical remission. The patient was still alive after more than 30 months of follow-up [4]. The investigational agent, pralatrexate (30 mg/m2) when given weekly with vitamin B12 and folic acid can result in remarkable clinical response with regression of skin tumours.

This tumours is very rare indeed with a very poor prognosis. Most of the patients do not survive the disease. The average survival was 14 months (range 1-10 months). For patients younger than 40 years, the survival was 38 months whereas for patients older than 40 years have a median survival of 10 months. This patient survived for one month after diagnosis. Kazakov reported a similar prognosis where patients had good general status at presentation but deteriorate rapidly in the course of the illness. He also reported a similar high incidence of association with myelodysplastic and myeloproliferative disorders in such patients [5].

CONCLUSION

BPDCN is an aggressive tumor that frequently presents in the skin, then rapidly and lethally progresses. While no effective therapy exists to date, early recognition and aggressive initial therapy such as bone marrow transplant is warranted as it may improve the patients' prognosis.

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