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CASE REPORT

CD4+ CD56+ Hematodermic Neoplasm Without Cutaneous Involvement

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Abstract CD4+/CD56+ hematodermic neoplasm is a recently recognized highly aggressive tumor presenting in skin, usually with lymph node and bone marrow involvement, often terminating in a leukemic phase. It has a distinct clinical presentation of primary skin lesions in the form of papules, nodules or bruise like areas. Bone marrow and peripheral blood involvement without skin involvement is a very rare phenomenon. We are reporting an interesting case where an elderly male, a known diabetic, when investigated for the cause of generalised weakness was found to have CD4+/CD56+ hematodermic neoplasm, the unusual feature being absence of any associated cutaneous involvement.

Introduction

CD4+/CD56+ natural killer hematodermic neoplasm variously known as blastic or blastoid (NK) cell lymphoma or tumours of plasmacytoid dendritic lineage, is a highly aggressive neoplasm with a rapidly fatal course. It was first described in 1994 by Adachi et al. [1]. Since then around 150 cases have been documented in the literature [2]. Majority (~90 %) of patients presents with asymptomatic solitary or multifocal skin lesions. Though low level bone marrow and peripheral blood involvement are seen in most of the cases but leukemic manifestation with extensive bone marrow involvement in absence of skin lesion is a very rare phenomenon [2].

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To our knowledge there are only two such documented cases, both been submitted in the 2005 Society for Hematopathology/European association for pathology workshop [2]. We are reporting one another case of CD4+/CD56+ hematodermic neoplasm with marked cytopenia and extensive bone marrow involvement without any associated skin lesions.

Case History

A 58-years-old male was admitted in the department of endocrinology of our institute with chief complaint of generalised weakness with off and on fever for 2 months. This patient was a known case of diabetes and was on strict glycemic control. The physical examination was normal except for the presence of marked pallor. There was no lymphadenopathy, splenomegaly or skin lesion. Peripheral blood examination revealed severe anemia (hemoglobin 5.1 g/dL), marked leucopenia (total leucocyte count 1.0×10^6/L) and thrombocytopenia (platelet count 85×10^9/L). Red cell morphology was microcytic and hypochromic. Hence a bone marrow examination was advised. Bone marrow aspiration was hypercellular and was predominantly composed of immature cells with plasmacytoid morphology, high nucleocytoplasmic ratio, moderate amount of cytoplasm, fine chromatin and single prominent nucleoli. Cytoplasmic vacuolation was also seen in some cells. Cytochemical stain for myeloperoxidase was negative. On immunophenotyping these immature cells were gated and were positive for CD4, CD56, CD45, CD33, HLA-DR. Other T and B cell markers were negative. Immunohistochemistry performed on sections of bone marrow biopsy revealed that the cells were strongly positive with antibody for CD68 (Fig. 1). Hence with all these features diagnosis of CD4+/CD56+ hematodermic

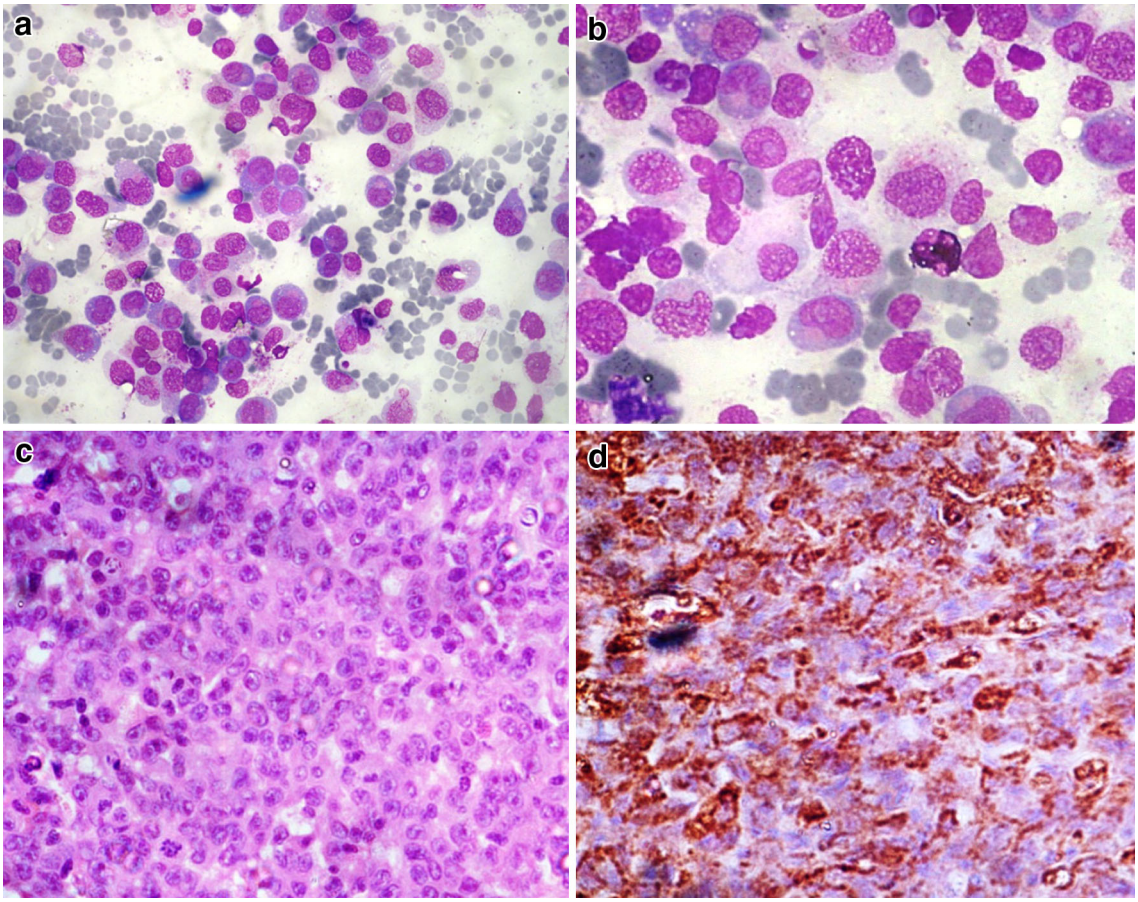

Fig. 1 **a** Medium sized blasts with plasmacytoid morphology, single prominent nucleolus and moderate amount of cytoplasm (Leishman stain; ×200). **b** Higher power view of same cells (Leishman stain; ×400). **c** Extensive bone marrow involvement by CD4+ CD56+ hematodermic neoplasm. **d** CD 68 expression in pDCs in bone marrow biopsy

neoplasm was made. The patient refused treatment and died within few months of diagnosis.

Discussion

For a long time there has been a debate regarding the true histogenesis of CD4+/CD56+ hematodermic neoplasm which is reflected in it's nomenclature as these are known as blastic or blastoid natural killer cell lymphoma, CD4+ CD56+ hematodermic neoplasm or tumors of plasmacytoid dendritic cell (pDC) lineage. Initially due to CD4 positivity a T cell lineage was hypothesised but later in 1990s a natural killer (NK) cell histogenesis was favoured based on CD56 expression, which was later found to be a non specific NK cell marker [3]. With the delineation of pDC by Grouard et al. [4] which express CD4, CD45, HLA-DR and CD123, more recently the World Health Organisation has proposed the term CD4+/CD56+ hematodermic neoplasm or early pDC leukemia/lymphoma for this neoplasm [5]. The number of well documented cases of HN in literature is around 150, with four largest series representing more than half of all published cases [6–8].

This neoplasm predominantly arises in elderly male and presents asymptomatic skin lesions which may be solitary or multifocal. In 50 % cases skin lesion may be the only extramedullary manifestation. Lymph node involvement (40–50 %) is relatively common, however splenomegaly (∼20 %) and systemic B symptoms are very rare. Low level bone marrow and peripheral blood involvement is seen in almost all cases along with skin lesions [2]. But best to our knowledge there are only two documented cases till date showing extensive bone marrow involvement without any cutaneous manifestation. Both of these cases were submitted to the 2005 Society for Hematopathology/ European association for Hematopathology workshop (cases 50 and 77) [2]. In cases with skin lesion diagnosis is based on skin biopsy which shows immature cells with blastic morphology. But in cases like our case diagnosis can only be achieved by immunohistochemical or immunophenotypical methods. When these immature cells express CD4 and CD56 in absence of lineage specific

markers of T cells and B cells then diagnosis of HN can be made. The extended phenotype is CD45RA+/HLA-DR+/CD123+/CD116. A subset of HN may also express CD68. The recent development of pDC associated immunomarkers has led to improved specificity in the diagnosis of HNs. The most important of these is CD123 (interleukin, IL-3, receptor α chain) and TCL1 (an Akt kinase regulator and lymphoid proto-oncogene) [4, 9].

Based on the emergence of typical myelomonocytic leukaemia in a subset of HN cases, these tumors may also have monocytic or multilineage potential. This is consistent with the finding that DC2s are sometimes increased in patients with myelomonocytic leukaemia and can be derived from monocytes in vitro under certain conditions and may undergo conversion in vivo to myeloid-type DCs. Hence they can also express CD33 variably as in our case [10, 11].

The common differential diagnosis in the reported setting is acute leukemia and myelodysplastic syndrome but they can be ruled out by simple cytochemical stain like myeloperoxidase because expression of MPO should always rule out the diagnosis of HN.

The prognosis is poor with median survival of about 14 months with a little better prognosis in patients where disease is localised to skin. Treatment is conventional chemotherapy for acute myeloid leukemia which generally shows a good response initially followed by quick and fatal relapse in extracutaneous sites such as bone marrow. Alternative therapies are immunomodulation or immunotherapy with interleukin-3 or with anti-CD123 antibody.

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