Case Report

Citation: Panditha Gunwardena VC, Siribaddana AD & Hilmi AJ, et al., 2021. Case of a young girl with marked bone marrow plasmacytosis, Sri Lanka Journal of Medicine, 30(1), pp 117-121
DOI: <http://doi.org/10.4038/sljm.v30i1.280>

Case of a young girl with marked bone marrow plasmacytosis.

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Abstract

Marked plasmacytosis in the bone marrow is a rare finding in young people. If present it is secondary to an underlying disease condition. Castleman disease is a rare form of lymphoproliferative disorder. Due to its rarity, it is not frequently considered in the differential diagnosis of lymphadenopathy. As in any other lymphoproliferative disorder Castleman disease can also be associated with various immune mediated cytopenia. This case report is on a teenager with persistent lymphadenopathy of whom the presence of marked bone marrow plasmacytosis led to the diagnosis of plasma cell type Castleman disease which went into complete remission with single agent vincristine and radiotherapy with subsequent severe immune thrombocytopenia during follow up.

Keywords: *Plasmacytosis, Castleman, lymphadenopathy, vincristine, polyclonal*

INTRODUCTION

Marked plasmacytosis in bone marrow is a rare finding in young people. We report a case of a teenager with persistent lymphadenopathy of whom the detection of the underlying disease was aided by the presence of marked plasmacytosis in the bone marrow.

CASE REPORT

A 17-year-old girl presented with left cervical lymphadenopathy for few weeks' duration. There was no fever, cough, throat pain, oronasal or

otolaryngeal symptoms. The nodes were small and non-tender. No other lymphadenopathy. No lung signs or hepatosplenomegaly. Complete blood count, erythrocyte sedimentation rate and C-reactive proteins were normal. Cervical lymph node biopsy was performed and histology showed reactive changes. Viral serology for Epstein-Barr was negative. Anti-nuclear antibody (ANA) was negative. Mantoux test was negative. Symptomatic treatment was given and she was discharged from the hospital.

During the next one-year period the lymph nodes gradually enlarged, and her general condition became poor. She developed chronic cough, nocturnal fever with sweating and weight loss. There was no hemoptysis. She was thoroughly investigated in the respiratory unit where ultra sound scan abdomen was normal and the neck scan showed left anterior and upper cervical lymphadenopathy with largest measuring 36x18 mm. ESR was 148 mm. Chest x-ray was normal. Mantoux test and sputum acid fast bacilli were negative. Serology for Epstein-Barr and Human immune deficiency viruses were negative. Contrast enhanced computed tomography did not show internal lymphadenopathy, hepatosplenomegaly, pleural effusions or ascites.

She underwent a repeat cervical lymph node biopsy which showed florid reactive lymphoid follicular hyperplasia and no evidence of toxoplasmosis, granulomata or malignancy. Serology for toxoplasma, ANA, anti-double stranded DNA and rheumatoid factor were

negative. It was decided to go ahead with a bone marrow aspiration and biopsy. Bone marrow aspiration revealed a marked increase in mature large plasma cells accounting for 50% of the nucleated cells [Figure 1]. Trephine biopsy showed that plasma cells were collected mainly around perivascular areas. No atypical lymphoid infiltrates, parasitic inclusions, granulomata or caseation. Immunohistochemistry revealed both kappa and lambda positive polyclonal plasma cells. Serum protein electrophoresis and immunofixation showed marked polyclonal hypergammaglobulinemia [Figure 2] with the presence of both kappa and lambda fractions. With these new findings the lymph nodes were re-analyzed with deep sections. There was a dense diffuse infiltrate of mature plasma cells in the interfollicular region which confirmed plasma cell variant of Castleman disease [Figure 3] Complete diagnosis was made as multicentric Castleman disease (MCD) with pseudo myelomatous plasmacytosis in the marrow.

Figure 1: Bone marrow with marked plasmacytosis

Figure 3: Lymph node showing dense infiltrate of mature plasma cells in the interfollicular region

Figure 2: Serum protein electrophoresis (SPE) with marked hypergammaglobulinaemia

Patient was treated with single agent vincristine 1.2 mg/m² weekly for 18 weeks and radiotherapy to cervical lymph nodes - 40 gray 20 fractions over 4 weeks. During the period of chemotherapy her hepatorenal functions, white cell and platelet counts remained normal. She had a moderate anemia with negative direct Coomb's test which was managed with symptomatic blood transfusions. She tolerated the treatment well and went into complete remission.

After 2 years, she developed multiple petechiae all over the body. No lymphadenopathy. On further investigation she was found to have severe thrombocytopenia with counts below 10x10⁹/L. Coagulation profile was normal. Bone marrow aspiration and biopsy were repeated which showed normal active marrow with normal megakaryocytes and normal plasma cells which confirmed immune mediated thrombocytopenia (ITP). She developed excessive bleeding from the marrow biopsy site as well as heavy menstrual bleeding and required platelet and blood transfusions. She was treated with intravenous immunoglobulin and prednisolone. During the course of prednisolone, she developed marked hyperglycaemia with severe acidosis and diagnosed to have diabetic ketoacidosis and required intensive care. She recovered from all the complications and went into complete remission of ITP. She is off steroids and now on regular follow up.

DISCUSSION

Castleman Disease (CD) is a rare, lymphoproliferative disease with incompletely understood etiology [1][8][9]. The disease was first reported by Dr Benjamin Castleman in 1954 [3][9]. It is considered a distinct clinico-pathological entity with massive non-malignant proliferation of lymphoid tissue [1][9]. Four etiological hypotheses, including autoimmune, autoinflammatory, neoplastic, and pathogenic mechanisms are proposed as pathophysiology of CD, which are now being actively investigated by Castleman Disease Collaborative Network (CDCN) [10]. Bulk of the evidence points toward an autoimmune aetiology or faulty immune

regulation [1][9]. It has broad spectrum of symptoms and a course of disease [1].

CD exhibits several histological patterns. The hyaline vascular variant is characterized by abnormal follicles with regressed germinal centers surrounded by widened mantle zones composed of small lymphocytes in an onion ring-like arrangement. The plasma cell variant is characterized by hyperplastic germinal centers and a massive accumulation of polyclonal plasma cells in the interfollicular region. Marked vascular proliferation in the interfollicular region is present in both variants. The bone marrow may show marked increase in polyclonal plasma cells as occurred in our patient [7]. Mixed forms demonstrate the presence of both hyaline vascular and plasma cell elements [4].

CD consists of two clinical categories; unicentric (UCD) and multicentric (MCD). Unicentric form is usually asymptomatic and presents as a localized mass. Multicentric type is characterized by systemic symptoms, fever with chills, anemia, generalized lymphadenopathy and with a more aggressive behaviour. Our patient had multicentric disease with systemic symptoms and involvement of multiple cervical lymph nodes. MCD commonly occurs at fourth to sixth decade. Our patient's age is an unusual age for the disease.

Bone marrow involvement in MCD and characteristic morphologic findings within the bone marrow is reported in Human Herpes virus (HHV)-8 and HIV positive patients [7]. It is not common to encounter in a 17-year-old in the absence of HIV.

Treatment of MCD is challenging, and outcomes can be poor because no uniform treatment guidelines exist [10]. Monoclonal antibodies to interleukin-6 and its receptor, allow for more targeted disease-specific intervention with improved response rates and more durable disease control [11]. Low-dose single-agent chemotherapy such as intermittent etoposide/rituximab/ vinblastine or combination chemotherapy, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) [11] [12] are used when anti-IL-6 therapies are not

available. There are no reports of single agent vincristine therapy which was used in our patient. She went into complete remission with vincristine and radiotherapy.

Disease free survival over first three years in HIV negative plasma cell MCD is 46%. [5] Patients with HHV8-associated MCD show a higher incidence of non-Hodgkin lymphoma. In HIV-associated MCD patients, lymphoma incidence was reported to be 15-fold higher than in the general HIV-positive population. [6]. Rarely MCD transform to multiple myeloma.

CD is known to be associated with various autoimmune manifestations, immune cytopenia including ITP which is thought to be due to disordered immune regulation [2] [8]. Our patient developed ITP after 2 years from the first presentation.

CONCLUSION

It is important to consider CD in the differential diagnosis of patients presenting with persistent lymphadenopathy. Bone marrow assessment to look for polyclonal plasmacytosis is essential in suspected plasma cell type CD. With accurate diagnosis and appropriate therapy their survival is improved. Single agent therapy with vincristine followed by radiotherapy is an effective therapeutic modality. Immune mediated cytopenia can complicate the course of the disease.

Author declaration

Acknowledgements

Staff of Haematology, Histopathology and Biochemistry laboratory for the laboratory work up done to arrive at the diagnosis.

Author Contributions

All authors had access to the data, and participated in writing the paper. In addition,

1) Dr A Siribaddana - Initial detailed diagnostic work up of the patient, inward management and clinic follow up.

2) Dr Vishaka P Gunawardena - Performing bone marrow and trephine biopsy and detecting marked bone marrow plasmacytosis. Management of the haematological complications of the disease and clinic follow up for the same. Final manuscript writing

3) Dr Palitha Rathnayake - Reporting the lymph node biopsy to confirm the diagnosis of Castleman's disease.

4) Dr A J Hilmi - Oncological management of Castleman's disease and clinic follow up

Dr Chamari Weerasooriya - Daily management of the patient while in the Haematology ward.

Funding sources

None

Availability of data and materials

All the relevant data of this case is stored at the department of Haematology, National Hospital Kandy

Ethics approval and consent to participate

collected a consent letter from the patient.

Competing interests

The authors declare that they have no conflicts of interest.

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