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Case Report

A male with longstanding anaemia eventually diagnosed with Waldenström Macroglobulinaemia

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Introduction

Waldenström macroglobulinemia is a distinct clinicopathological entity defined as a B-cell neoplasm characterized by lymphoplasmacytic infiltration of the bone marrow. It is associated with IgM paraproteinemia [1]. We present a male with longstanding anaemia was diagnosed with Waldenström macroglobulinemia, and made a good recovery following plasmapheresis and chemotherapy.

In 1944, the Swedish oncologist Jan G. Waldenström described a clinical syndrome characterized by a haemorrhagic diathesis with epistaxis, leucopaenia, hypofibrinogenaemia, lymphadenopathy and the presence of an abnormal protein of large molecular weight associated with neoplastic plasma cells in the bone marrow. He entitled the syndrome "incipient myelomatosis." Since his original description, many studies have been conducted on the presence, chemical characteristics and implications of abnormal serum proteins in a variety of disorders. Particular interest has been shown in the abnormal proteins observed during the course of multiple myeloma, leukaemia, lymphomas and liver diseases. In the American literature, however, only a few cases have been reported that fit the syndrome now known as “macroglobulinaemia of Waldenström” [2].

Our patient presented with anaemia, and constitutional symptoms, with lymphadenopathy and hepatomegaly and was ultimately found to have Waldenström macroglobulinemia.

Case report

A 62-year-old man presented with fatigue and weight loss for four months. He was a diabetic of one year, on tolbutamide, with well controlled sugar levels. During the previous three months he had been investigated for persistent anaemia which was detected following admission for evacuation of a traumatic subdural haematoma in fronto-parietal region. He revealed a history of night sweats but no fever. There was no history of spontaneous bleeding. His appetite was good. On examination, he was moderately pale with generalized lymphadenopathy. His blood pressure and cardio

respiratory examination were normal. He had a 4cm hepatomegaly but no other organomegaly. Fundal examination showed venous dilatation. Initial investigations revealed a hypochromic microcytic anaemia with a haemoglobin of 6.9g/dL and a high RDW. Serum ferritin was normal and the reticulocyte count was 0.77%. No haemoglobinopathy was detected on high-performance liquid chromatography (HPLC). The direct antiglobulin test was negative. Serum bilirubin and haptoglobin were within the normal range. The ESR was 116mm/1st hour. His renal and liver functions were normal. Serum protein electrophoresis revealed a monoclonal band in the gamma region and immunofixation revealed IgM, kappa light chain bands as shown in figures 1 and 2.

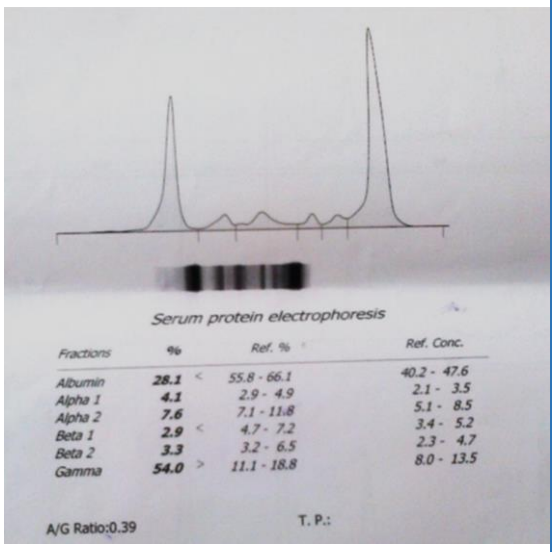


Figure 1: Monoclonal band in the gamma region with a paraprotein level of >47g/l.

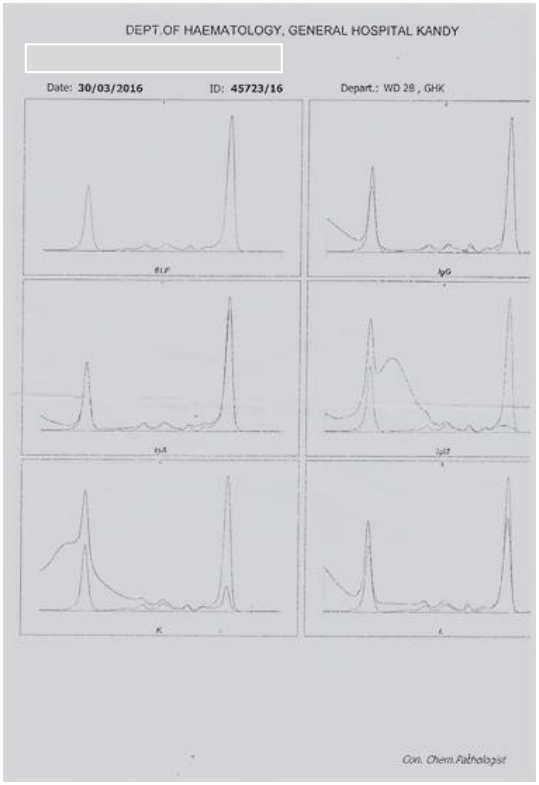


Figure 2: Immunofixation showing IgM band and kappa light chain band

Bone marrow biopsy revealed diffuse infiltration by small to medium sized lymphocytes, plasma cells and lymphoplasmacytoid cells noted in 85% of the biopsy area, suggestive of Waldenström Macroglobulinemia. Immunohistochemistry of the trephine biopsy was compatible with a CD20 positive interfollicular B-Cell lymphoma. Lymph node biopsy also showed a B-Cell Non-Hodgkins Lymphoma which was, again, compatible with the diagnosis of Waldenström Macroglobulinemia. Ideally, immunophenotyping for antigenic expression patterns such as CD5 (-),CD10(-), CD103(-), CD23 (-), CD25 (+), CD27 (+), FMC7 (+), CD138 (-) should be performed to exclude other lymphoplasmacytoid lymphomas.

Criteria to diagnose Waldenström Macroglobulinemia were fulfilled by the demonstration of an IgM monoclonal protein, along with histological evidence of infiltration of the bone marrow by clonal lymphoplasmacytic cells in line with the diagnosis of

lymphoplasmacytic lymphoma (LPL) in our patient. FISH analysis was performed to exclude chronic myeloid leukemia (CLL) as shown in figure 3.

ACCESSION NO : **0002PD031466** AGE : 62 Years SEX : Male DATE OF BIRTH :

DRAWN : 10/04/2016 00:00 RECEIVED : 12/04/2016 16:20 REPORTED : 15/04/2016 17:41

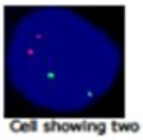
REFERRING DOCTOR : CLIENT PATIENT ID : RB21/11-04/2016

Test Report Status Final	Results	Biological Reference Interval	Units

CLL PANEL FLUORESCENCE IN SITU HYBRIDIZATION

DEL13Q

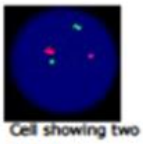
SPECIMEN	BONE MARROW
CLINICAL INDICATIONS	--
TOTAL NUMBER OF CELLS	200
13Q14 DELETION	08
NORMAL	192
INTERPRETATION	NEGATIVE FOR DELETION OF THE 13q14.3 LOCUS.



Cell showing two orange and two green signals, indicating negative for deletion of the 13q14.3 locus.

DEL TP53

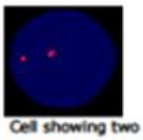
TOTAL NUMBER OF CELLS	200
TP53 DELETION	04
NORMAL	196
INTERPRETATION	NEGATIVE FOR DELETION OF THE TP 53(17p 13.1) LOCUS.



Cell showing two orange and two green signals, indicating negative for deletion of the TP 53 (17p 13.1) locus.

DELATM

TOTAL NUMBER OF CELLS	200
ATM DELETION	06
NORMAL	194
INTERPRETATION	NEGATIVE FOR DELETION OF THE ATM (11q22.3) LOCUS.



Cell showing two orange signals , indicating negative for deletion of the ATM (11q22.3) locus.

TRISOMY CEP 12

TOTAL NUMBER OF CELLS	200

Page 1 Of 2

Figure 3: Fluorescent in-situ hybridization (FISH) analysis

Discussion

Waldenström macroglobulinemia is a mature B-cell lymphoid neoplasm composed of small B-lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow and sometimes lymph nodes and, very rarely, the spleen, which does not fulfill the criteria for the other small B-cell lymphoid neoplasms [3]. It is a diagnosis of exclusion and when associated with IgM monoclonal gammopathy, it is termed Waldenström macroglobulinemia.

Although the overall incidence of Waldenström macroglobulinemia remains steady, a significant increase in incidence has been seen, over the past 20 years, in whites and in those aged 70 to 79 years. It has a male preponderance [4]. Its occurrence is highest among white people and it is rare in other population groups [5].

The aetiology of Waldenström macroglobulinaemia is unclear, and no specific environmental or occupational exposure, including smoking, has been linked to this entity. In most of the cases, it appears to be sporadic; however, there have been reports of familial clustering.

Waldenström macroglobulinaemia can involve various organs, such as the skin, gastrointestinal tract, kidney, liver, adnexae, minor salivary gland, central nervous system, and retina. Features relating to monoclonal gammopathy, including hyperviscosity, cryoglobulinaemia and amyloidosis, may be observed [6]. The symptoms and signs are mainly due to lymphocytic infiltration of marrow leading to cytopaenias, especially anaemia, which commonly manifests as fatigue and constitutional symptoms such as fever, night sweats or weight loss. Infiltration of peripheral tissues, leading to lymphadenopathy and hepatosplenomegaly, occurs in 20–30% of patients. The consequences of IgM in the circulation manifest as symptoms of hyper viscosity, mainly neurological, which includes blurring of vision, headache, and rarely stroke and coma [7]. The association of macroglobulinaemia with neurological symptoms such as polyneuropathy has been referred to as the Bing-Neel syndrome [8.

Attempts to better describe Waldenström macroglobulinemia have been made recently by both the WHO Lymphoma Classification, a consensus group formed at the Second International Workshop on Waldenström Macroglobulinaemia and the Mayo Clinic [5].The consensus group formed restricts the diagnosis exclusively to cases with lymphoplasmacytic lymphoma and an IgM monoclonal protein and it eliminates the requirement for either a minimum amount of marrow involvement by lymphoplasmacytic lymphoma or a threshold concentration of IgM in the serum. In contrast, Mayo Clinic criteria require at least 10% marrow involvement by lymphoplasmacytic lymphoma in asymptomatic patients. To diagnose the condition it is expected to identify an M-band in serum protein electrophoresis with bone marrow biopsy evidence of lymphoplasmacytic infiltration. Our patient fulfilled the above diagnostic criteria. Flow cytometry and FISH are supportive investigations [9].

The disease is incurable with current therapy, and the decision to treat patients as well as the choice of treatment can be complex. There should be a risk-adopted approach and there are recommendations on timing and choice of therapy 5]. The consensus panel convened during the Second International Workshop on Waldenström Macroglobulinemia agreed that initiation of therapy was appropriate for patients with constitutional symptoms, presence of progressive, symptomatic lymphadenopathy or splenomegaly, presence of anaemia with a haemoglobin value of 10 g/dL or lower or a platelet count lower than 100×10^9/L and certain complications such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency or symptomatic cryoglobulinaemia. These patients should be treated

with a dexamethasone, rituximab and cyclophosphamide regimen. Any patient with symptoms of hyper viscosity should first be given plasmapheresis. It was recommended that patients with IgM mono clonal gammopathy of undetermined significance (MGUS) and smoldering Waldenström macroglobulinemia be observed without treatment and be evaluated every six months [5]. The median period of survival ranges between 5 and 10 years [7].

Conclusion

As our patient was medically fit and had a good performance score, he was commenced on bendamustine, rituximab and dexamethasone. Chemotherapy was given in six monthly cycles together with assessment of paraprotein levels and he showed a good response to treatment and is being followed up with chemotherapy cycles at the Haematology Unit, Teaching Hospital Kandy.

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