Leishmaniasis Mimicking Lymphoma and/or Liver Cirrhosis

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Abstract:

A 76-year-old man was admitted to hospital with fever, weight loss, pancytopenia, hepatosplenomegaly and a double monoclonal component IgM-IgG-k, suggesting a diagnosis of myeloma. Bone marrow and liver biopsies disclosed the presence of Donovan bodies, and the titre of anti-Leishmania antibodies was extremely high. After treatment with liposomal amphotericin B, the titre of antibodies fell considerably, while monoclonal components, pancytopenia and clinical symptoms slowly disappeared. Polyclonal γ-globulins are made of innumerable monoclonal components, one of which can appear as a recognizable band and be misdiagnosed as myeloma when representing the high titre of an antibody directed towards a specific antigen.

Keywords: Leishmaniasis, multiple myeloma, lymphoma, liver cirrhosis, M-components

Introduction

The appearance of monoclonal components in serum focuses attention on multiple myeloma or lymphoma.
Pancytopenia associated to spleen/liver enlargement has a broad differential diagnosis, further complicated by its association with a double monoclonal component. We report herein a patient exhibiting these features, in whom the diagnosis could have been missed or delayed if pancytopenia, unreported in the area where the patient was living, had not been taken into consideration, and the M-components had not been linked to the presence of a high titre of antibodies caused by the offending agent.

Case description
A male Caucasian patient, aged 76, was admitted to an Internal Medicine ward in March 2009 because of worsening dyspnoea, fatigue, and ankle oedema.

The referral diagnosis was monoclonal gammopathy of undetermined significance (MGUS) with double IgG-IgM-k components, increased γ-globulins and refractory pancytopenia with multi-linear dysplasia (Table 1).

<table>
<thead>
<tr>
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<th>5690 mg/dl</th>
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<tbody>
<tr>
<td>IgG</td>
<td>362 mg/dl</td>
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<tr>
<td>IgA</td>
<td>210 mg/dl</td>
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<tr>
<td>Pk</td>
<td>1400 mg/dl</td>
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<tr>
<td>λP</td>
<td>525 mg/dl</td>
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<tr>
<td>Uk</td>
<td>42.2 mg/dl</td>
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<tr>
<td>Uλ</td>
<td>27.8 mg/dl</td>
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<tr>
<td>Pβ₂ microglobulin</td>
<td>16,578 ng/ml</td>
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<tr>
<td>Uβ₂ microglobulin</td>
<td>21,565 ng/ml</td>
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<tr>
<td>Daily proteinuria</td>
<td>417 mg</td>
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<tr>
<td>INR</td>
<td>1.32</td>
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<tr>
<td>aPTT</td>
<td>46.8 s</td>
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<tr>
<td>p 14</td>
<td>+</td>
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<tr>
<td>p 16</td>
<td>+</td>
</tr>
<tr>
<td>Ab anti-Leishmania</td>
<td>1/5120</td>
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Table 1: Data obtained on patient’s admission, referring to measurements indicated by the international nomenclature, as explained in the text.

These findings were interpreted as suggestive of myelodysplasia associated to plasmacytosis and marrow...
fibrosis (Fig. 1).

Nuclear magnetic resonance (NMR) disclosed increased liver size, left lobe hypertrophy, portal vein of 20 mm diameter and spleen of 20×20 cm.

Liver elastometry measured a stiffness of 27.7 KPa, compatible with liver cirrhosis.

Liver biopsy evidenced pericellular and perisinusoidal fibrosis, with regenerative nodules, and a polymorphous portal and periportal inflammatory infiltrate, formed by granulocytes and macrophages (Fig. 2).

At higher magnification, numerous Donovan bodies were recognized inside liver cells and macrophages (Fig. 3).

The bone marrow biopsy, re-examined, also showed Donovan bodies inside histiocytes (Fig. 4). The titre of anti-Leishmania antibodies was executed at the “Istituto Superiore di Sanità”, Rome (Italy), and was found positive at a 1/5120 dilution, associated to a strong positivity to p14 and weak positivity to p16 by Western blot.

Leishmaniasis is unreported in residents in Piedmont (Italy). However, the patient spent the summer months in the county of Savona (Liguria, Italy), where an epidemic source of infection is known and Phlebotomus papatasi, a vector insect of Leishmania, is present along the coast. The patient was treated with liposomal amphotericin B (Ambisome) 5 mg/kg/day for 5 consecutive days and then once weekly for 5 weeks.

The disease remitted completely: IgG fell to 1430, IgM to 115, IgA to 220 mg/dl and antibody titre to 1/2520. The hepatosplenomegaly reverted to normal, and so did the abnormal liver exams, while pancytopenia
disappeared.

**Discussion**

The differential diagnosis of this patient was difficult, as several entities are characterized by hepatosplenomegaly, pancytopenia fever and a double IgM-IgG monoclonal component. Felty’s syndrome was unlikely because of the absence of rheumatoid arthritis, while a T-hepatosplenic lymphoma, although rare, was possible. However, this and angioimmunoblastic lymphoma are aggressive, leading to a progressive disruption of liver structure, attended by jaundice and ascites. In contrast, the present patient displayed a more chronic course, more typical of T-large granular lymphocytes leukaemia, a disease associated with rheumatoid arthritis and red cell aplasia, which were not present in this case. Hairy cell leukaemia (HCL) fitted the picture, but hairy cells were not found in his peripheral blood. The monoclonal components were suggestive of other B-cell lymphomas, namely prolymphocytic leukaemia, because of liver/spleen involvement. However, the typical plasmacytoid lymphocytes were not observed in the patient’s peripheral blood.

Hepatosplenic T-cell lymphoma (HSTL) is a neoplasm of mature T cells that infiltrates the sinusoids of the spleen,
liver and bone marrow. Most patients exhibit marked hepatosplenomegaly without lymphadenopathy at physical examination, and the blood exams demonstrate thrombocytopenia. Other common findings include systemic B symptoms (weight loss, fever, night sweats), anaemia, neutropenia and abnormal LFTs. The diagnosis is based on the accumulation of malignant atypical lymphocytes expressing CD2/CD3/CD7/CD16, γ/δ-T-cell receptors and/or α/β-T-cell-receptors. This condition was ruled out because of the absence of the typical histological pattern.

Angio-immunoblastic T-cell lymphoma (AITL) is one of the more common peripheral T-cell lymphomas and is thought to come from peripheral CD4-positive T cells, perhaps corresponding to a subset of follicular helper T-cells. Patients typically present with acute onset of generalized lymphadenopathy, hepatosplenomegaly and systemic B symptoms with or without a rash, occasionally associated with autoimmune haemolytic anaemia, plasmacytosis or polyclonal hypergammaglobulinaemia. The diagnosis of AITL is best made by excisional biopsy of a lymph node. These two last entities are aggressive, leading to a progressive disruption of liver structure, attended by jaundice and ascites, whereas the present patient displayed a more chronic course.

T-large granular lymphocyte (LGL) leukaemia is a clonal disease of the large granular lymphocyte characterized by peripheral blood and marrow lymphocytic infiltration with LGLs, splenomegaly and neutropenia. LGL leukaemia can be of T- or NK-cell lineage. Even though monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma have been described in association with LGL leukaemia, this disease was ruled out because it requires association with rheumatoid arthritis and red cell aplasia.

HCL causes splenomegaly (which may be massive), systemic complaints, bruising and bleeding secondary to severe thrombocytopenia, and recurrent infections secondary to granulocytopenia and monocytopenia. A diagnosis of HCL is confirmed when the abnormal cells display pan-B cell antigens (e.g. CD19/CD20/CD22) along with positivity for CD103/CD11c/CD25. The clinical features HCL fitted our patient, but hairy cells were not found in his peripheral blood.

Prolymphocytic leukaemia (B-PLL) is a rare B-cell neoplasm comprising prolymphocytes, typically with involvement of the peripheral blood, bone marrow and spleen. It is most common in elderly Caucasians. A T-cell variant has been reported.

Falciparum malaria, nowadays unheard of in Italy in people who have not travelled to endemic areas, was ruled out by repeated peripheral blood smears. Mycobacterium avium complex is being reported in HIV-positive patients, but the patient was negative. Typhoid fever was ruled out by the negative serum reaction and the absence of roseola. Brucellosis causes leukocytosis, whereas the patient was leukopenic. Peripheral leukocytosis could have been expected also in portal vein phlebitis or abscess formation in the context of liver cirrhosis. Having ruled out all the above possibilities, biclonal multiple myeloma was the only possibility left, although this constitutes only 1% of all myelomas. However, the progressive liver disease and worsening of clinical conditions, pancytopenia, spleen enlargement, fever with marked sweating and clinical signs suggestive of a systemic infection called for a unifying infectious hypothesis. L. L. Lieshmaniasis, though unheard of in this
geographic area, did satisfy the clinical/laboratory picture, with the exception of the monoclonal bands, unless these were due to a markedly high titre of anti-Leishmania antibodies, detected during the switch from IgM to IgG.

In conclusion, although leishmaniasis in northern Italy is increasingly reported only in travellers from endemic areas and countries\textsuperscript{10}, and is thus not usually suspected, it was indeed the correct diagnosis in this patient. The monoclonal bands, a “red herring” in the differential diagnosis, were in fact due to the high titre of specific anti-Leishmania antibodies, “frozen” in the blood sample during the switch from IgM to IgG.

This case demonstrates how an apparently clear diagnosis of B-cell lymphoma (including initial multiple myeloma or Waldenström’s disease) and/or liver cirrhosis could mimic a reversible condition.

After all, “polyclonal” γ-globulins are made of an almost unlimited number of small monoclonal components, each specific for an offending agent. It should come as no surprise that, during the acute antibody response to an antigen, the monoclonal component could be detected, suggesting multiple myeloma or lymphoma. This M-component should disappear with the drop in antibody titre, as happened in our patient. In fact, a similar case due to Babesia infection has been previously reported, suggesting that protozoan infections may be more likely to cause pseudo-myeloma or -lymphoma.

Learning Points

- Rare diseases, although rare, do occur, even when not included in the differential diagnosis.
- The differential diagnosis of fever, leucopoenia and liver/spleen enlargement includes leishmaniasis.
- A double IgM-IgG monoclonal antibody should raise suspicion of a recent severe infection.
- There are cases of apparent liver cirrhosis, with highly suggestive elastometry stiffness values, which are reversible.

References


