Case Report

Multiple myeloma in a patient with fever of unknown origin and cholestasis

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ABSTRACT

THE DIFFERENTIAL DIAGNOSIS OF FEVER of unknown origin includes infectious diseases, malignancies and connective tissue diseases. Multiple myeloma is not usually included in the differential diagnosis, nor is it considered a frequent cause of cholestasis in the absence of amyloidosis. We report a case of multiple myeloma in a patient presenting with a long-standing fever and cholestasis. The patient underwent a long and unfruitful series of diagnostic procedures, including liver biopsy. The clue to the diagnosis, established with a marrow biopsy, was the presence of a paraprotein in the serum.

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A 61-year-old man was admitted to hospital with a fever of unknown origin that had persisted for 4 months. His past medical history included a healed gastric ulcer, chronic allergic rhinitis and surgical correction of an inguinal hernia and varicocele. The patient did not take drugs or drink alcohol. Four months earlier he had experienced weakness and fever (39–40°C) in the late afternoons, along with coughing, profuse sweating, an erythematous rash, but no shivering. These symptoms lasted, with fluctuations, for the entire 4-month period. Two courses of antibiotics (azythromycin and ceftriaxone) had no effect on any of the symptoms. He was then admitted to another hospital for a 4-week stay, where a comprehensive evaluation was performed. Routine blood tests, including white blood cells, liver and kidney panels, electrolytes and urinalysis were normal, except for elevated erythrocyte sedimentation rate, γ-glutamil transpeptidase and ferritin. CT scans of the thorax and abdomen, an MRI of the abdomen and ultrasounds of the abdomen and the heart (transthoracic and transesophageal) were all unremarkable. Upper GI endoscopy and bronchoscopy were performed, along with a double-contrast barium enema and a radionuclide bone scan, all of which were negative. Blood cultures, serology for hepatitis A, B and C, Epstein-Barr virus, Cytomegalo virus, Toxoplasma gondii, M. bovis and plasmodia were all negative. Tests for antibodies to brucella, salmonella and autoreactive antibodies (ANA, anti-ENA, anti-ds-DNA, AMA, ASMA, p-ANCA and c-ANCA) were absent. Tuberculosis skin tests were negative. He was discharged after 4 weeks without a definite diagnosis, but still complaining of fever. At discharge, a 30-day course of oral methylprednisolone (32 mg daily) was highly effective at relieving all of the symptoms; unfortunately, the fever, coughing and sweating recurred as soon as the course was completed.

The patient was admitted to our hospital for a reassessment of his fever of unknown origin. He appeared relatively well, except for the presence of high fever spikes (up to 39.5°C) in the evenings. He was not jaundiced, and bilirubin, liver transaminases and calcium levels were normal. Smears for malaria and serology for HIV were negative. Relevant laboratory investigations (including tests for rheumatic factors and cryoglobulins) showed increases of acute-phase reactants with mild normocytic anemia. Alkaline phosphatase and γ-glutamil transpeptidase were both elevated, suggesting cholestasis (Table 1). A liver biopsy showed a normal hepatic structure, with lipofuscin into the hepatocytes, minimal siderosis and the absence of copper, all consistent with cholestasis. No signs of diffuse or granulomatous infiltrates were detected. Protein electrophoresis revealed an alpha-2 peak with a broad gamma band. Immunofixation revealed an immunoglobulin-G-k monoclonal component (Fig. 1); Bence-Jones proteinuria was absent. Radiological study of the entire skeleton was unremarkable. A biopsy of the bone marrow revealed aggregates of polymorphic lymphocytes,

Table 1: Abnormal laboratory results

Component	Results
Erythrocyte sedimentation rate, first hour	118 mm
C-reactive protein	1898.6 μmol/L
Red blood cell count	3.9 x 10^{12}/L
Hemoglobin	102 g/L
γ-glutamil transpeptidase	203 U/L
Alkaline phosphatase	767 U/L
Ferritin	131 μg/L
Iron	25.06 μmol/L
Transferrin	1.55 g/L
Immuglobin G	18.63 g/L
α_2-globulins	13 g/L
Fibrinogen	39.03 μmol/L
b_2-microglobulin	1966.95 μmol/L

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accounting for 35% of the marrow cellularity (a normal reading is < 10%); the aggregates stained positively for kappa light chain and MUM 18 and negatively for lambda light chain, cytocheratins, CD68/PGM1, triptase and CD34. This pattern is consistent with monoclonal β-lymphocitic expansion with kappa clonality, compatible with the histologic diagnosis of a low-grade nodular myeloma (Fig. 2). The patient was then given vincristine, doxorubicin and dexamethasone. He was afebrile from the first course of chemotherapy. His fever subsided on the fourth day of treatment and has not recurred. He was seen 12 months after treatment and has remained well.

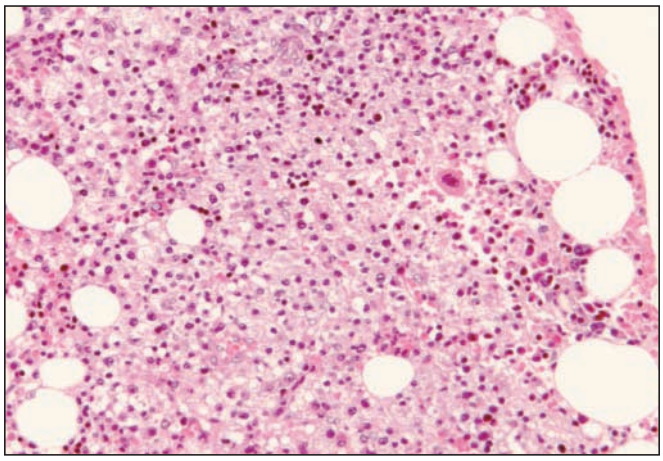

Fig. 1: Bone marrow aspirate immunofixation showing an immunoglobulin-G-k monoclonal component.

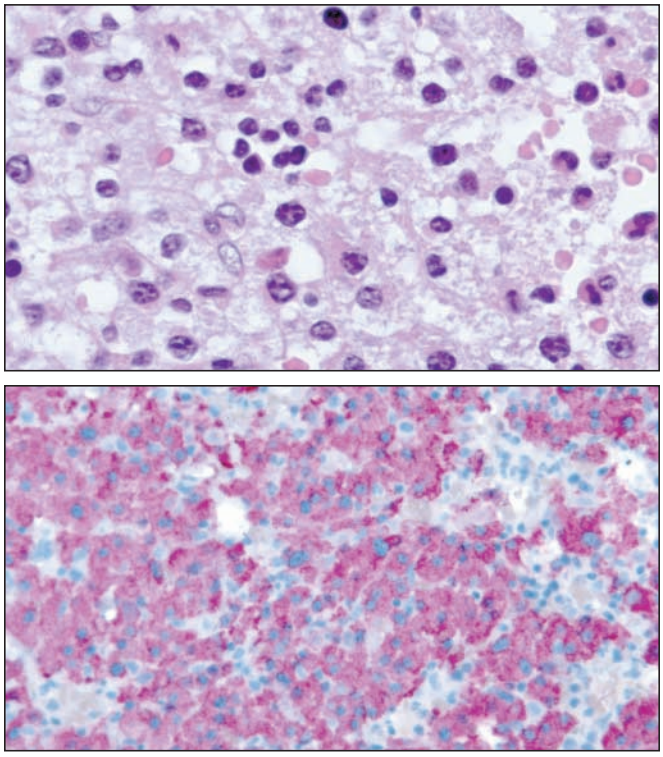

Fig. 2: The first panel shows bone marrow aspirate, stained with hematoxilin-eosin. The second panel shows immunohistochemical stain with MUM-18.

Discussion

To our knowledge, only 1 case of multiple myeloma presenting with fever and cholestasis has been previously reported.[1] Overall, few cases of fevers of unknown origin and myeloma have been reported, including a recent series of 9 cases out of 5523 (0.2%) patients retrospectively identified with a fever of unknown origin over a period of more than 25 years.[2] Our case fulfils all the diagnostic criteria of fevers of unknown origin,[3] and the fever completely disappeared with successful chemotherapy. Myeloma can cause hepatic amyloidosis, which in turn can result in severe cholestasis with jaundice and often liver failure and renal impairment.[4–8] In our case, however, there were no overt signs of amyloidosis, liver failure or kidney involvement. A prospective study is needed to establish the true prevalence of multiple myeloma in patients with fever of unknown origin or cholestasis. For the time being, we propose that at least a basic search for monoclonal proteins (i.e., serum electrophoresis and Bence-Jones proteinuria) should be included as a part of the diagnostic algorithm of such patients.

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References

1. Vella FS, Barbara S, Giannelli G, Pesolo MT, Ingravallo G, Gentile A, et al. Case of multiple myeloma mimicking an infectious disease with fever, intrahepatic cholestasis, renal failure, and pulmonary insufficiency. Am J Hematol 2003;72:38-42.
2. Mueller PS, Terrel CL, Gertz MA. Fever of unknown origin caused by multiple myeloma: a report of 9 cases. Arch Intern Med 2002;162:1305-9.
3. Petersdorf RG. Fever of unknown origin: an old friend revisited. Arch Intern Med 1992;152:21-2.
4. Terada T, Hirata K, Hisada Y, Hoshii Y, Nakanuma Y. Obstructive jaundice caused by the deposition of amyloid-like substances in the extrahepatic and large intrahepatic bile ducts in a patient with multiple myeloma. Histopathology 1994;24:485-7.
5. Robles M, Navia-Osorio Garcia-Braga JM, Menendez Caro JL, Velasco Alonso J, Lopez Lagunas I. [Jaundice secondary to intrahepatic deposit of light chains as a presenting form of multiple myeloma.] An Med Interna 1994;11:74-6.
6. Yamamoto T, Maeda N, Kawasaky H. Hepatic failure in a case of multiple myeloma-associated amyloidosis (kappa-AL). J Gastroenterol 1995;30:393-7.
7. Licht A, Maurer R, Oelz O. Myeloma and severe cholestasis. Schweiz Med Wochenschr 1999;129:1201-4.
8. Arkenau HT, Widjaja A. [A rare case of cholestasis and macrohematuria in a 52-year-old patient.] Med Klin 2002;97:480-3.

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