A Healthy Young Man Presenting with Multiple Rib Fractures
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CASE
A 32-year-old, otherwise healthy man presented initially with right rib and sternal pain after lifting a heavy object. The patient also reported several rib fractures 1 year previously associated with coughing. On examination, the patient had bilateral rib tenderness. Chest x-ray revealed multiple healing fractures of the sixth, seventh, and eighth ribs. A bone scan demonstrated increased uptake in the sternum and bilaterally in the ribs.

A complete blood count was normal with the exception of a platelet count of 61 000/μL (reference interval, 130 000–440 000/μL). Alkaline phosphatase, creatinine, and calcium were within reference intervals. Total protein and albumin were 67 g/L (reference interval, 61–79 g/L) and 44 g/L (reference interval, 35–48 g/L), respectively. Ig concentrations were decreased: IgG 6.07 g/L (reference interval, 7.51–15.60 g/L), IgA 0.31 g/L (reference interval, 0.69–2.09 g/L), and IgM 0.10 g/L (reference interval, 0.48–2.74 g/L). We performed serum protein electrophoresis (SPEP)5 and immunofixation using the Sebia Hydrasys®. SPEP showed no monoclonal band in the /H9253 region but an explained band in the /H9252 region with a reduced /H9253-globulin concentration of 3.9 g/L (reference interval, 6–14 g/L). Serum immunofixation electrophoresis showed a prominent /H9252 monoclonal band in the β region and hypogammaglobulinemia. Immunofixation studies for IgG, IgA, and IgM were negative for the presence of monoclonal bands. β2-Microglobulin was increased at 3.51 mg/L (reference interval, <1.85 mg/L). Twenty-four-hour urine collection was significant for a total protein of 0.54 g/24 h (reference interval, <0.15 g/24 h); urine protein electrophoresis (UPEP) and immunofixation revealed 2 monoclonal λ light chain bands.

PATIENT FOLLOW-UP
A bone marrow biopsy revealed hypercellular marrow with markedly increased numbers of atypical plasma cells comprising 85% of the cell population. Chromosomal analysis demonstrated an abnormal karyotype with translocation between the long arms of chromosomes 11 and 14, suggestive of standard prognostic risk (1). Flow cytometry showed a monoclonal population of B lymphocytes with expression of surface IgD, λ light chain, plasma cell–associated antigen 1 (PCA-1), and CD38. Serum IgD was found to be 3.1 g/L (reference interval, 0.18 g/L), and IgE concentration was within reference intervals. The patient’s serum was sent to a reference laboratory for further workup for IgD and IgE immunofixation studies, which demonstrated an IgD λ monoclonal gammopathy migrating in the β region. Based on the clinical and laboratory findings, we made the diagnosis of IgD multiple myeloma.

The patient was initially treated with lenalidomide and dexamethasone. An autologous stem cell transplantation (ASCT) was performed after treatment with high-dose melphalan. After ASCT, serum IgD was 0.007 g/L (<0.18 g/L) and bone marrow biopsy showed 3%–5% residual λ monoclonal plasma cells. The patient was subsequently treated with thalidomide with good response. Repeat bone marrow biopsy performed 5 months after ASCT showed no evidence of residual monoclonal plasma cell population, and plasma IgD concentrations remained near 0.03 g/L.

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5 Nonstandard abbreviations: SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; ASCT, autologous stem cell transplantation.

QUESTIONS TO CONSIDER
1. List the significant and atypical findings in this case.
2. Given the patient’s SPEP and immunofixation results, what additional testing should be performed by the laboratory?
3. What is the differential diagnosis of a monoclonal band that shows staining for light chains, but not for IgG, IgA or IgM?
Approximately 8 months after ASCT, the patient developed multifocal bone pain and was found to have an increased serum IgD concentration of 0.54 g/L. Radiographic evaluation did not reveal the presence of lytic bone lesions. He was treated with bortezomib for 2 months, but continued to show increasing IgD concentrations up to 0.96 g/L. Chemotherapy was then changed to combination therapy of doxorubicin, vincristine, and dexamethasone. On this regimen, serum IgD declined over several months to 0.14 g/L with gradual resolution of bone pain.

**DISCUSSION**

**DIFFICULTIES IN THE DIAGNOSIS OF IgD MYELOMA**

IgD multiple myeloma represents approximately 2% of multiple myeloma cases (2, 3). Patients are usually younger than those with IgG or IgA myeloma (4–6) and are more likely to present with nonspecific systemic symptoms of fatigue, fever, and weakness. In the current case, clinical presentation was atypical due to the young age (32 years) and lack of systemic findings. A male:female ratio between 2:1 and 3:1 for IgD myeloma has been reported (4, 5, 7), compared with a 1:1 ratio seen in IgG myeloma or light chain disease. In addition to a small or absent M-spike on serum protein electrophoresis, laboratory findings that differentiate IgD myeloma from the more common IgG and IgA myelomas include the presence of a light chain predominance, as seen in our case, and higher rates of Bence Jones proteinuria (5, 7).

The initial workup of a suspected monoclonal gammopathy includes serum and urine protein electrophoresis. The vast majority of patients with IgG, IgA, or IgM myeloma show a monoclonal band on SPEP. Between 12% and 60% of patients with IgD myeloma show no monoclonal protein on SPEP or SPEP without a distinct monoclonal band in the region, and only monoclonal light chains were present on serum immunofixation. UPEP often reveals the presence of monoclonal light chains only. These laboratory findings—small or absent M-spike on SPEP and monoclonal light chain only on UPEP and immunofixation—are also consistent with light chain disease. Serum free light chain assays may detect increased concentrations of light chains in the serum but do not establish their monoclonality and cannot differentiate between light chain disease and IgD or IgE myeloma. In patients with monoclonal free light chains in the serum and/or urine, immunofixation is required to rule out IgD or IgE myeloma. Alternatively, as done in this case, determination of IgD and IgE concentrations can be used in combination with the findings of a monoclonal light chain with no corresponding IgG, IgA, or IgM band to aid in the diagnosis of a monoclonal IgE or IgD.

The majority of clinical laboratories do not include IgD in the initial workup of monoclonal gammopathies (6). Testing for IgD and IgE monoclonal gammopathy should be performed when a patient presents with a small or absent monoclonal M-spike on SPEP and a monoclonal light chain without a corresponding IgG, IgA, or IgM component are consistent with both light chain disease and IgD myeloma, and should prompt immunofixation for IgD.

**POINTS TO REMEMBER**

- Clinical features associated with IgD myeloma, as opposed to IgG or IgA myeloma, include young age of onset, rapid disease progression, and increased rate of amyloidosis and bone involvement.
- SPEP may reveal a small or absent monoclonal spike in IgD myeloma.
- Most laboratories do not routinely perform immunofixation for IgD or IgE. Reflex testing for IgD and IgE should be performed when serum immunofixation demonstrates a monoclonal light chain without a corresponding monoclonal IgG, IgA, and IgM band.
- SPEP without a distinct monoclonal band in the β or γ region and monoclonal light chains on serum or urine immunofixation without a corresponding IgA, IgG, or IgM component are consistent with both light chain disease and IgD myeloma, and should prompt immunofixation for IgD.
- Hypogammaglobulinemia is a common finding in multiple myeloma patients, and thus should raise the consideration for immunofixation studies. Furthermore, depressed concentrations of nonmonoclonal immunoglobulins are associated with adverse prognosis.
Commentary

David Sinclair*

This case report is a useful account of an unusual presentation of IgD myeloma. Because of the prognostic differences that exist between IgD myeloma and other more common forms of the malignancy, recognition of this paraprotein is important. Without the laboratorian’s involvement, this diagnosis can easily be delayed or missed.

The authors followed all of the steps that should be taken in a case such as this. They noted the polyclonal immune paresis although the globulin fraction was normal and proceeded to immunofixation of the serum because there was a small band in the β region. In my experience, a distinct band might not always be visible on simple electrophoresis, and therefore immunofixation is always indicated in cases where the polyclonal immunoglobulins are suppressed. Once a monoclonal light chain was identified, the authors were correct to look for IgD and IgE heavy chains—particularly so in this case, where monoclonal λ light chains are involved, given the preponderance of λ light chains in IgD myeloma. Examination of urine for the presence of Bence Jones proteinuria should be a mandatory procedure in cases like this.

A more general clinical point should be made about the investigation of anyone with a “pathological bone fracture.” The possibility of myeloma was not investigated earlier, although there was clear evidence of rib fractures a year previously, presumably because of the patient’s age and otherwise nonspecific symptoms. Regardless of the patient’s age, if there is a pathological fracture, an immunoglobulin profile then becomes an essential part of the workup of that patient.

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