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A 68-year-old woman with high serum protein and no symptoms

WHILE PERFORMING a routine annual checkup for a 68-year-old woman, a family physician notes that the patient's total serum protein level is high at 11.2 mg/dL. Her other laboratory values are unremarkable: her serum creatinine level is 1.1 mg/dL, calcium 9.1 mg/dL, and albumin 3.8 g/dL. Except for nonspecific arthralgias, the patient has no symptoms: no headache, no dizziness, no back pain, no visual disturbances, and no weight loss. Her physical examination is completely normal. An automated blood cell count and differential is normal; urinalysis reveals trace proteinuria.

The elevated total serum protein level leads the physician to order a serum protein electrophoresis, which shows a "spike" in gamma globulin (FIGURE 1). This elevation is known as an "M" (monoclonal) component, because it reflects the production of clones of one cell. It is also known as "monoclonal gammopathy," even if it involves an antibody other than gamma globulin.

The patient was told that she may have multiple myeloma and was referred for further evaluation.

WHAT DIAGNOSTIC TESTS ARE REQUIRED?

1 Which one of the following is not appropriate as a further diagnostic study?

- ❑ Bone scan
- ❑ Urine protein electrophoresis
- ❑ Serum protein immune electrophoresis
- ❑ Bone marrow biopsy

This case scenario is not uncommon. The patient may have multiple myeloma, but the data presented are not enough to make the diagnosis, which requires the criteria listed in TABLE 1.

The workup for monoclonal gammopathy

The diagnostic workup for monoclonal gammopathy and possible multiple myeloma involves the sequence of steps listed below. A primary care physician who finds any elevation in total protein without a concomitant elevation in serum albumin should order a serum protein electrophoresis and immune protein electrophoresis. If an M component is found, then a radiologic assessment of the skeleton should be performed and the patient then referred to a hematologist for a bone marrow biopsy and further hematologic evaluation.

Electrophoresis for multiple myeloma and its related disorders is performed in two parts: (1) serum protein electrophoresis, to determine if there is an M component; and (2) immune protein electrophoresis, to confirm and identify the subtype of immunoglobulin to which the M component belongs.

Urine protein electrophoresis is required to detect certain fragments of immunoglobulins called Bence Jones proteins—monoclonal light chains with unique thermal properties.

A SELF-TEST of clinical recognition

If serum protein is elevated but albumin is normal, obtain protein electrophoresis

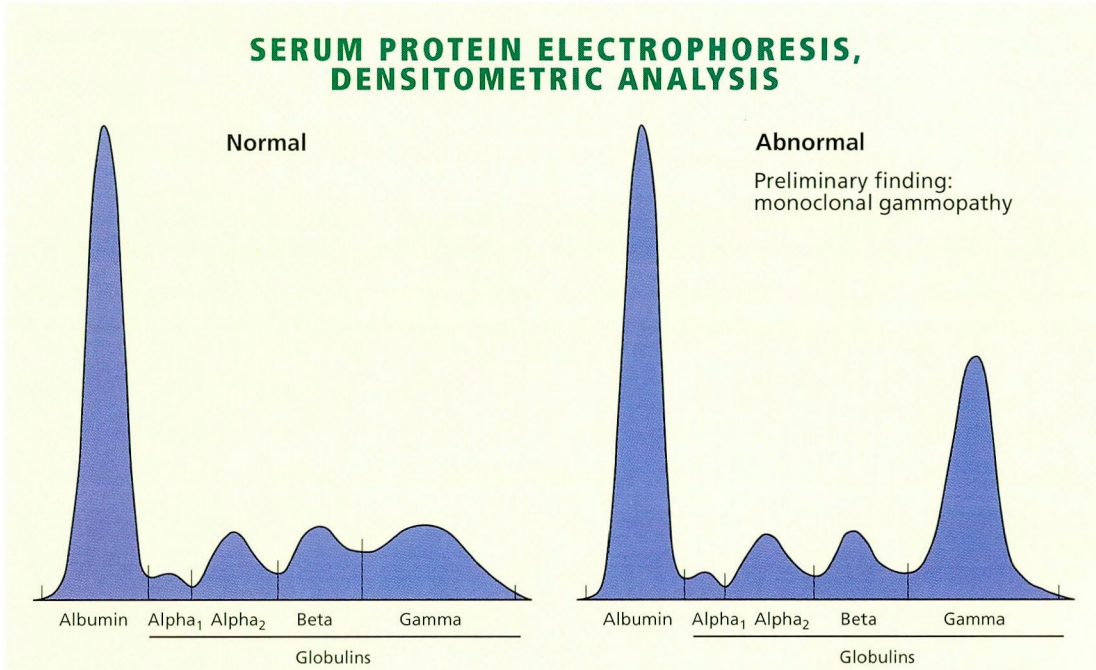

FIGURE 1 The area under the curve corresponds to the serum concentration. The tracing on the left is normal. The tracing on the right shows a spike in the gamma globulins, indicating a monoclonal (M) component, also known as monoclonal gammopathy.

Characteristically, they precipitate at 40 to 60°C, dissolve at 100°C, and reprecipitate with cooling. They are best detected by collecting a 24-hour sample, an aliquot from which is concentrated and then subjected to electrophoresis.

Bone marrow biopsy is also indicated, to differentiate between multiple myeloma and its related disorders by determining the percentage of plasma cells in the bone marrow. The pattern of infiltration may also have a prognostic significance.

A radiologic survey of the entire skeleton (skeletal survey) is mandatory. Conventional roentgenograms may show "punched out" lytic lesions, osteoporosis, or pathological fractures, most frequently in the skull, vertebrae, ribs, and pelvis.

Bone scans do not detect these abnormalities as well as conventional roentgenograms do, because lytic lesions do not take up technetium well. Thus, a bone scan would not be required.

If there is a monoclonal protein elevation, order a skeletal survey and consult a hematologist

HOW OFTEN DOES MONOCLONAL GAMMOPATHY REFLECT MULTIPLE MYELOMA?

2 What percentage of patients with newly discovered monoclonal gammopathy have multiple myeloma?

- ❑ 100%
- ❑ 75%
- ❑ 50%
- ❑ < 25%

Not every patient with monoclonal gammopathy has multiple myeloma. One series[1] described more than 800 patients with monoclonal gammopathy, of whom only 14% had multiple myeloma, while 60% had monoclonal gammopathy of undetermined significance (which is discussed in detail below). The remainder had amyloidosis, macroglobulinemia, or other lymphoproliferative disorders.

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE: COMMON, ASYMPTOMATIC

This patient underwent a skeletal survey, which showed no lytic lesions. A bone marrow biopsy showed 2% plasma cells (normal: < 5%). Serum immune electrophoresis showed a monoclonal immunoglobulin G (IgG) spike of 1.8 g/dL (normal: 717–1411 mg/dL and polyclonal, not monoclonal). Urine protein electrophoresis showed no monoclonal spike.

On the basis of this workup, this patient does not have multiple myeloma, but does have an M component in the absence of features of multiple myeloma, macroglobulinemia, amyloidosis, or other related diseases. This condition is called "monoclonal gammopathy of undetermined significance" (MGUS) (TABLE 2).

Monoclonal gammopathy of undetermined significance is common and increases in prevalence with age—up to 10% to 14% in patients older than 70 years. It is invariably diagnosed in asymptomatic patients on a routine serum chemistry evaluation. The elevation of monoclonal protein is modest by definition in MGUS; as a result, hyperviscosity does not occur. Usually the elevated protein is of the IgG type, although the immunologic subtype has little prognostic significance. Because patients with MGUS tend to be elderly and have associated diseases, many already have osteoporosis and renal dysfunction, sometimes making it difficult to differentiate between MGUS and multiple myeloma unless the diagnostic criteria listed above are carefully applied.

TABLE 1

DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA

Both of the following:

- Bone marrow plasma cells > 10%
- Extramedullary plasmacytoma

***Or* one of the above, plus any two of the following:**

- Serum M protein (usually defined as a level > 3 g/dL)
- Urine M protein
- Lytic bone lesions

TABLE 2

CHARACTERISTICS OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

- Serum M protein < 3 g/dL
- Bone marrow plasma cells < 5% of total marrow cells
- Little or no urine M protein
- Absence of lytic bone lesions, hypercalcemia, or renal insufficiency
- Stability over time

WHAT IS THE NATURAL HISTORY OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE?

3 With further follow-up, this patient's condition will most likely:

- ❑ Remain the same
- ❑ Evolve into multiple myeloma
- ❑ Evolve into macroglobulinemia
- ❑ Evolve into lymphoma

The natural history of monoclonal gammopathy of undetermined significance has been well studied[1–5]; in retrospective published reports, large numbers of patients were followed for long periods. In one series,[2] 241 patients (median age 64 years) were followed for a median of 22 years (range 20 to 35 years), during which 47% died of unrelated diseases, 19% had stable monoclonal gammopathy, 10% had significant increases in their M component levels (> 3 g/dL), and 24% developed frank myeloma or a related disorder (16% multiple myeloma, 3% amyloidosis, 3% macroglobulinemia, and 2% lymphoma).

MGUS is common, especially in older patients

Therefore, although monoclonal gammopathy of undetermined significance usually remains stable, approximately one in four patients eventually develops a serious hematologic disease, a probability that mandates detecting MGUS and designing an appropriate follow-up strategy. If a patient is destined

to develop a hematologic malignant disease, we can intervene more effectively if we detect it earlier.

WHAT IS THE OPTIMAL FOLLOW-UP SCHEDULE?

4 What is the best follow-up schedule for a patient with monoclonal gammopathy of undetermined significance?

- ❑ Monthly for 2 years
- ❑ Every 3 to 6 months for 10 years
- ❑ Every 3 to 6 months, indefinitely
- ❑ No further follow-up is needed

The interval between recognition of an M component and the diagnosis of multiple myeloma or a related disorder ranges from 2 to 29 years, a finding that indicates that patients with an apparent monoclonal gammopathy of undetermined significance must be followed indefinitely. Thus, we would recommend evaluating the patient every 3 months after the diagnosis of MGUS for 2 years. After this, if the patient appears to have stable disease, follow-up may be decreased to every 6 months.

At each visit, we recommend performing:

- A history and physical examination.
- A measurement of M component by serum protein electrophoresis.
- A complete blood count with differential.
- Serum protein, albumin, creatinine, and calcium measurements.

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