CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises
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CASE 39-1992
PRESENTATION OF CASE

A 49-year-old woman was admitted to the hospital because of severe abdominal pain, vomiting, and weight loss.

The patient was well until six years earlier, when splenomegaly was found. The hematocrit ranged up to 55.1 percent, the white-cell count to 11,500 (11.5×10⁶ per liter), and the platelet count to 717,000 (717×10⁶ per liter). A naphthotomometric examination and echocardiographic study were negative. A diagnosis of polycythemia vera was made; phlebotomy was performed on three occasions, and the hematocrit thereafter remained normal.

Five years before admission alopecia developed. One year later the patient began to experience progressive numbness of the toes, feet, and shins, with Raynaud’s phenomenon, fatigue, polyarthralgia, and mild hyperpigmentation of the forehead; splenomegaly persisted. The erythrocyte sedimentation rate ranged from 70 to 80 mm per hour. A test for antinuclear antibodies was positive in a titer of 1:64 (homogeneous); tests for rheumatoid factor, anti-native DNA antibodies, and cryoprecipitate were negative, and the results of repeated complement studies were normal. Microscopical examination of a needle-biopsy specimen of the bone marrow and a computed tomographic (CT) scan of the abdomen were negative except for the presence of hepatosplenicomegaly. Motor and sensory-nerve conduction studies and an electromyographic examination showed a severe, symmetric distal peripheral neuropathy. A diagnosis of systemic lupus erythematosus was made; treatment was begun with prednisone and hydroxychloroquine, although the latter medication was later discontinued because of abdominal discomfort. Repeated abdominal CT scans revealed no evidence of a malignant tumor. Pleural effusions were noted intermittently on radiographic studies within the year before entry. During that year the patient had recurrent episodes of depression and was twice admitted to hospitals for antidepressant medication. Eight months before admission she began to have visual loss and experienced several bouts of diplopia that lasted for approximately half an hour. Further evaluation disclosed bilateral papilledema. A magnetic resonance imaging scan of the cranium was negative, and a lumbar puncture yielded normal cerebrospinal fluid although the initial pressure was 280 mm of water. A diagnosis of pseudotumor cerebri was made, and acetazolamide was added to the medication. Four months before entry intermittent abdominal pain developed, with nausea and vomiting.

Three weeks before admission the patient was referred to this hospital, where physical examination showed that the blood pressure was 120/75 mm Hg, she was cachectic, with generalized hyperpigmentation and prominent hepatosplenicomegaly. An electrocardiogram showed sinus tachycardia at a rate of 103, with left posterior hemiblock and clockwise rotation. The findings on review of multiple recent imaging studies obtained elsewhere included a small left pleural effusion and a retrocardiac infiltrate on an x-ray film of the chest. A CT scan of the abdomen (Fig. 1) revealed bilateral pleural effusions; moderate ascites; peripancreatic, paraaortic, and retrocaudal lymphadenopathy; marked enlargement of the spleen, which contained calcifications; hepatomegaly; and enlargement of the uterus, which contained a leiomyoma.

On the day before entry the patient awoke with severe nausea and upper abdominal pain and vomited bile-stained liquid on approximately five occasions. She passed a formed brown stool. After dinner she vomited and began to have severe pain in the left upper abdominal quadrant that radiated to the back, punctuated by spasms of more severe, “knife-like” pain in the left upper quadrant that lasted one to five minutes and occurred five to six times per hour. She returned to this hospital.

The patient’s husband and three children were well.

Figure 1. Computed Tomographic Scan of the Abdomen, Disclosing Marked Splenomegaly with a Small Punctate Calcification (Arrow), Scattered Retroperitoneal Lymph Nodes, and a Small Amount of Ascites.
She had a history of a "nervous stomach," for which phenobarbital was prescribed during her adolescence. A small duodenal ulcer was found 10 years before admission. She had irregular menses for two years. She had lost 13.6 kg during the six months before entry and 2.7 kg in the immediately preceding two weeks. A progressive decline in the serum albumin had been noted over the past several months. There was a history of heart disease in both parents; her father had diabetes mellitus, and her mother and a sister had severe lactose intolerance; six other siblings were well.

The temperature was 37°C, the pulse was 110, and the respirations were 20. The blood pressure was 110/60 mm Hg.

On physical examination the patient was cachectic and had mild discomfort from abdominal pain. Generalized hyperpigmentation was present. A lymph node, 3 cm, was palpated in the right axilla and another lymph node, 1 cm, was felt in the left axilla. The edge of the liver descended 7 cm below the right costal margin, and the spleen descended 8 cm below the left; there was mild, diffuse abdominal tenderness; no mass was palpated. The fingers were cold and mildly cyanotic, and there was trace pedal edema; no digital clubbing was seen; the peripheral pulses were normal. The patient was fully alert and oriented. Cranial-nerve functions were preserved. Muscle strength and sensation were intact except that muscle power was graded 4/5 in the lower extremities, with impaired sensation.

The urine gave a + test for protein; the sediment contained 15 white cells, 2 red cells, 8 hyaline casts, and a few bacteria per high-power field. The hematocrit, white-cell count, differential count, platelet count, prothrombin time, and partial-thromboplastin time were normal. The creatinine, glucose, calcium, phosphorus, other electrolytes, bilirubin, and a random cortisol level were normal. The serum aspartate aminotransferase, creatine kinase, alkaline phosphatase, amylase, and the dehydrogenase were normal. A test for beta-human chorionic gonadotropin was negative. Additional laboratory findings are presented in Table 1. An electrocardiogram showed sinus tachycardia at a rate of 108; the R-wave axis was +131 degrees, and clockwise rotation was present; the appearance was unchanged in comparison with an electrocardiogram obtained several weeks earlier. Radiographs of the chest revealed elevation of the right hemidiaphragm; a density lateral to the heart filled the right cardiophrenic angle; the left costophrenic angle was blunted, a finding consistent with a small pleural effusion; the remaining lung fields were clear. X-ray films of the abdomen disclosed marked enlargement of the liver and spleen; the pattern of bowel gas was normal. X-ray films of the bones were normal; calcified lymph nodes were observed in the abdomen and pelvis.

Fluids and methylprednisolone were administered by vein, and meperidine was injected intramuscularly as needed for pain. The nausea and vomiting ceased; the patient remained afebrile. Examination with a fiberoptic esophagogastroduodenoscope showed mild, diffuse gastritis with bile-stained secretions that had a pH of 4.0; the duodenum was normal except for enlargement of the ampulla of Vater and a polyp, 9 mm, just distal to the ampulla, which was removed. Microscopic examination of biopsy specimens disclosed that the duodenal polyp was a hamartoma; a minute fragment of the ampulla of Vater contained fibroglanular tissue with mucinous metaplasia and chronic papillitis; specimens of the gastric antrum and the duodenum showed no abnormality; no amyloid was seen, and there was no evidence of Whipple's disease, parasitic infestation, or neoplasm.

On the third hospital day physical examination remained unchanged except that the abdomen was nontender. A culture of urine obtained on admission yielded abundant Escherichia coli. Trimethoprim-sulfamethoxazole was begun. An upper gastrointestinal series with small-bowel study revealed that the esophagus was normal; the stomach and duodenum appeared normal except for compression of the stomach by the large liver and spleen; barium passed rapidly through the small bowel and appeared in the cecum in approximately 10 minutes; the visible portions of the cecum appeared normal. A later enteroclysis examination of the small bowel showed no abnormality. Tests for antinuclear antibodies and for antibodies to native DNA were negative.

A laboratory report was received.

### Differential Diagnosis

**Dr. David Steinberg***: This 49-year-old woman was cachectic and ill after a six-year history of a puzzling systemic disorder that was initially diagnosed as polycythemia vera. The findings included a severe symmetric distal peripheral neuropathy, generalized hyperpigmentation of the skin, lymphadenopathy, hepatosplenomegaly, ascites, pleural effusions, polyarthralgias, Raynaud's phenomenon, and pseudotumor cerebri.

May we review the radiologic studies?

**Dr. Joseph T. Ferrucci, Jr.**: A section from the CT scan of the abdomen obtained three weeks before admission (Fig. 1) shows considerable hepatomegaly and enlargement of the spleen to four or five times its usual size, with a 1-cm punctate area of calcification visible within it. Other pertinent findings are a small amount of ascitic fluid in the flanks and a number of small retroperitoneal lymph nodes. A representative

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**Table 1. Additional Laboratory Findings.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>66 mm/hr</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>36 mg/100 ml (13 mmol/liter)</td>
</tr>
<tr>
<td>Protein</td>
<td>6.6 g/100 ml</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.7 g/100 ml</td>
</tr>
<tr>
<td>Globulin</td>
<td>3.9 g/100 ml</td>
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radiograph of the chest reveals no obvious air-space disease or gross pleural effusion. The architecture of the bones is normal, with no focal lytic or blastic lesions.

DR. STEINBERG: Did the CT scan show the high attenuation of the liver that is seen with excess iron deposition?

DR. FERRucci: No.

DR. STEINBERG: The challenge is to find the systemic illness that will best explain the unusual collection of findings in this case.

A low-grade lymphoma is a possible, although unlikely, diagnosis. It would explain the hepatosplenomegaly and lymphadenopathy. The sensorimotor peripheral neuropathy could be explained as a paraneoplastic process. However, transient pleural effusions, Raynaud's phenomenon, pseudotumor cerebri, and generalized hyperpigmentation of the skin are not easily explained by a diagnosis of lymphoma. Also, when pursued by an assiduous physician, lymphoma rarely remains undiagnosed for six years.

Sarcoidosis could also account for the hepatosplenomegaly and lymphadenopathy. Although uncommon, peripheral neuropathy and an elevated spinal fluid protein level can be found in patients with sarcoidosis.\(^1\) It is difficult to interpret the arthralgias, but sarcoidosis can involve the joints. Dermal granulomas can be seen in sarcoidosis, but not generalized hyperpigmentation. Pleural effusion is rare in sarcoidosis. Although the absence of bilateral hilar lymphadenopathy does not exclude sarcoidosis, it leaves me with no compelling reason to make that diagnosis.

Peripheral neuropathy, dermal melanosis,\(^2\) abdominal pain, and a psychiatric disturbance, such as depression, are features of this patient's illness that have been described in variegate porphyria. Peripheral neuropathy also occurs in association with that disease, but in contrast to the history in this case it is usually preceded by attacks of abdominal pain or mental disturbance and the upper limbs are usually most affected.\(^3\) Although hyperpigmentation was described in this patient, there is no mention of the bulbar, eruptions, and ulcers that follow minor trauma to light-exposed skin that characterize the dermal lesions of variegate porphyria. The failure of phenobarbital, which was given to this patient, to precipitate an attack further lessens the likelihood of variegate porphyria but does not exclude the diagnosis.\(^4\) Also, no family history of porphyria was mentioned, and many other findings in this patient would not be explained by that diagnosis.

The diagnosis of polycythemia vera six years before admission was a reasonable but not established diagnosis. Except for a uterine leiomyoma, which has been associated with an increased red-cell mass in some patients,\(^5\) there was no obvious reason for secondary erythrocytosis. The combination of an increased red-cell mass and splenomegaly has been accepted as sufficient for the diagnosis of polycythemia vera. Although a hematocrit of 55 percent in a woman suggests an increased red-cell mass, the red-cell mass was never measured directly in this patient. A decreased plasma volume or a difference between the peripheral hematocrit and the total body hematocrit can result in spurious erythrocytosis. The slightly elevated white-cell count and the elevated platelet count added to the probability of polycythemia vera, but these findings are not specific. Correction of the erythrocytosis with only three phlebotomies casts some doubt on the diagnosis, but in a menstruating woman it could be explained by iron deficiency. Other explanations for the transient nature of the erythrocytosis might include the development of an unrecognized second illness that inhibited erythropoiesis or, less likely in such a short time, the onset of postpolycythemic myeloid metaplasia.\(^6\)

Myeloid metaplasia could have developed, however, by the time of her admission several years later. Some of the findings at that time could be explained by extramedullary hematopoiesis. Lymphadenopathy has been described in a minority of patients with myeloid metaplasia.\(^7,8\) Although clinically important lymphadenopathy is unusual, it has been described.\(^9\) Extramedullary hematopoiesis has been found in many organs, including the liver, spleen, and other abdominal viscera and the pleura,\(^10\) and could explain at least in part the hepatosplenomegaly, pleural effusions, and ascites. The argument for extramedullary hematopoiesis is weakened by the absence of some of the important signs of myeloid metaplasia. The patient did not have anemia, an almost invariable finding in myeloid metaplasia.\(^10\) Also, she did not have the characteristic leukoerythroblastic blood smear. A bone marrow biopsy might have been helpful, but we are told only that the results of one performed four years earlier were normal.

Abdominal pain, ascites, hepatomegaly, splenomegaly, nausea, and vomiting, which occurred during the last hospital admission, are seen with occlusion of the hepatic veins, the Budd–Chiari syndrome.\(^11\) If she had polycythemia vera, this diagnosis should be considered. In one review of 253 patients with hepatic vein thrombosis\(^11\) the most common underlying illness was polycythemia vera.

Some of the unusual features of this patient's illness are not readily explained by the diagnosis of polycythemia vera. Although peripheral neuropathy has been described in association with polycythemia,\(^12\) it is uncommon. Pinkness and venous distention may be seen on examination of the optic disk, but pseudotumor cerebri is not a typical finding.\(^13\) Patients with erythrocytosis may have a ruddy, plethoric complexion, but this woman is described as having generalized hyperpigmentation at a time when her hematocrit was normal. Although she may have once had erythrocytosis and thrombocytosis, it is difficult to invoke polycythemia vera or a subsequent myeloid metaplasia as the sole explanation for her complex clinical picture.

Some of the findings in this case suggest hemochromatosis. Hyperpigmentation of the skin in hemochromatosis may be the result of deposition of both iron and melanin. Hepatosplenomegaly, arthralgias, ab-
dominal pain, and ascites may be manifestations of hemochromatosis. The absence of a family history of hemochromatosis might simply reflect the fact that the diagnosis is often overlooked. However, the CT scan did not show the high attenuation in the liver that is demonstrated in excess iron deposition, and we do not have the benefit of serum iron or ferritin values. Moreover, a diagnosis of hemochromatosis leaves many features unexplained.

Raynaud’s phenomenon, arthralgias, and distal motor weakness are seen in systemic sclerosis (scleroderma). The weakness is often the result of disuse atrophy or a primary myopathy, but neuropathy has been reported. Hyperpigmentation is a feature of scleroderma, but this patient did not have the characteristic thick, hard skin. Also, she did not have esophageal motility dysfunction, which occurs in about 75 percent of the cases. I do not find a diagnosis of systemic sclerosis satisfying.

Could the diagnosis be amyloidosis? This patient’s hepatosplenomegaly and lymphadenopathy could have been the result of amyloid infiltration. However, lymphadenopathy is uncommon in amyloidosis, and this patient’s spleen was larger than the typical spleen involved by amyloidosis. Peripheral neuropathy was one of the first manifestations of her illness and is the initial manifestation in 17 percent of patients with amyloidosis, which is associated with a distal symmetric, progressive neuropathy that can be painful. Most patients with amyloid neuropathy have a monoclonal protein that is usually a lambda light chain. An immunoelectrophoresis is not mentioned in this case record. This patient had both proteinuria, which is a common manifestation of amyloid nephropathy, and arthralgias, which could be ascribed to early amyloid arthropathy. She had alopecia and increased skin pigmentation, which have been observed in amyloidosis; however, she did not have any of the other dermal manifestations of amyloidosis, such as purpura, ecchymoses, waxy nodules, and thickened skin. Results of laboratory tests are nonspecific for amyloidosis, and ultimately a microscopic diagnosis is required. A small-bowel biopsy was negative for amyloid deposition, leaving it only a theoretical possibility.

In 1984 Nakanishi and his colleagues reported from Japan 102 cases of an unusual systemic disorder that they called the “Crow–Fukase syndrome,” naming it after early reporters of the syndrome. The syndrome has also been called the PEP syndrome (a peculiar progressive polyneuropathy associated with pigmentation, edema, and plasma-cell dyscrasia), “Shimpo’s syndrome,” and the “Takatsuki syndrome.” In the United States it has been more popularly referred to as the POEMS syndrome — polyneuropathy (P), organomegaly (O), endocrinopathy (E), M proteins (M), and skin changes (S). Not every patient, however, has all the findings, and the acronym does not encompass every manifestation of this remarkable disorder. I believe that this patient had the POEMS syndrome. I shall discuss the findings by going through the acronym letter by letter, and then I shall discuss the other manifestations of the syndrome.

In some reviews, polyneuropathy has been reported in 100 percent of patients with the POEMS syndrome, but its absence has also been noted. The polyneuropathy presents initially or early in the course as a progressive distal, symmetric sensorimotor deficit, which spreads proximally. Weakness in the arms and legs can be profound and accompanied by muscle wasting. Motor and sensory nerve-conduction velocities are greatly slowed. Nerve biopsies reveal degeneration of myelin sheaths and axons. Cranial-nerve involvement is rare. These findings are similar to those in this patient except that normal cerebrospinal fluid is unusual for the syndrome. An elevated cerebrospinal fluid protein level was found in one series in 93 of 96 patients evaluated, and not uncommonly the level was more than 200 mg per 100 ml. Typically, the cerebrospinal fluid cell count is normal. Organomegaly refers to the hepatomegaly, splenomegaly, and diffuse lymphadenopathy found in 82 percent, 39 percent, and 65 percent, respectively, of patients with the POEMS syndrome, and all these findings were seen in this patient.

Failure of multiple endocrine organs is common in the POEMS syndrome. Gonadal failure with amenorrhea and impotence, gynecomastia, primary hypothyroidism, and diabetes have been reported. Elevated prolactin and estrogen levels have been found. The only possible endocrine abnormality in this patient, irregular menses, could have been age-related or caused by her debilitated condition. Although most patients with the syndrome have an endocrine abnormality, not all do, and its apparent absence in this woman does not exclude the diagnosis.

An M component is found in 60 to 75 percent of the patients, with IgG slightly more common than IgA. In contrast to M components in multiple myeloma, in which kappa light chains outnumber lambda light chains about 2 to 1, the vast majority of M components in the POEMS syndrome have lambda light chains. These abnormal proteins may have a role in the pathogenesis of the disorder. Polyclonal hyperglobulinemia and the POEMS syndrome have been reported in patients exposed to toxic substances, such as organic solvents and agricultural chemicals. The normal total globulin level in this patient does not exclude the POEMS syndrome, because M protein levels can be low.

Generalized hyperpigmentation of the type seen in this patient has been described in more than 90 percent of patients with the POEMS syndrome. Other dermal abnormalities include hypertrichosis, with coarse, dark hair primarily on the extensor surfaces, white nails, hyperhidrosis, and skin thickening, which might be confused with scleroderma. Alopecia, which was one of the earliest abnormalities mentioned in this case, is not included in most reviews. Digital clubbing and cutaneous angiomas, which were not present in this patient, have been reported. Cyano-
sis, which was seen in this case, is another feature of the syndrome. Idiopathic skin flushing mimicking the carcinoid syndrome and dermal mastocytosis have also been reported.

Several features that are seen in patients with the POEMS syndrome but that are not included in the acronym were seen in this patient. Edema, pleural effusions that can be transient, and ascites that can be refractory to treatment are not uncommon. It has been suggested that these features result from an increase in capillary permeability. Raynaud's phenomenon, which this patient had, is also associated with the POEMS syndrome.

Computed tomographic examination of the abdomen showed an enlarged spleen with calcification. Splenic calcification is seen in tuberculosis, histoplasmosis, and brucellosis. This patient was not febrile, and the clinical picture did not suggest an infectious disease. Splenic calcification is also seen with splenic infarcts and hemangiomata and in Castlemann's disease, a disorder with pathological findings similar to the lesions seen in some patients with the POEMS syndrome. Therefore, it may not be necessary to invoke another diagnosis to explain the splenic calcification.

Although I concluded earlier that this woman's illness could not be well explained by the diagnosis of polycythemia vera alone, the finding of an elevated hematocrit early in the course of her illness is probably not irrelevant because the association of polycythemia and thrombocytosis with the POEMS syndrome has been well described, and polycythemia, as in this patient, has preceded the diagnosis of the POEMS syndrome. Papilledema with increased intracranial pressure without apparent structural abnormality (pseudotumor cerebri) is common in the POEMS syndrome. It developed in 56 of 91 patients (62 percent) described by Nakanishi et al. Swelling of the optic disk, the result of an infiltrative orbitopathy, has also been reported. Finally, this patient had mild proteinuria. Although it is a nonspecific finding and the creatinine level was normal, a microangiopathic glomerulopathy is yet another manifestation of the POEMS syndrome.

The POEMS syndrome is a rare disorder, although with greater awareness more cases are being recognized. The frequency among men is greater than that among women, and the age at the time of onset ranges from 27 to 80 years. The average age is 46 years, about the age of this patient; most patients are in their late 30s or 40s. Data on survival are limited, but the course can be prolonged.

The POEMS syndrome is not a final pathological diagnosis. One must ask what underlying illness can produce a disorder with such protean manifestations. A distal symmetric peripheral polyneuropathy similar to that seen in the POEMS syndrome has been described in about 20 percent of patients with osteosclerotic myeloma. Many patients with osteosclerotic myeloma and peripheral neuropathy have been reported to have a systemic illness that resembles the POEMS syndrome. In one series of patients with the POEMS syndrome the clinical manifestations of those with and without sclerotic bone lesions were similar. It is postulated that substances elaborated by malignant plasma cells inhibit the activity of trophic hormones, stimulate melanin secretion, have angiogenic activity, and stimulate both red-cell and platelet production. The causative role of the plasma cell is supported by the finding that the POEMS syndrome may regress slowly if there is a solitary lesion that can be removed or irradiated. The response to systemic chemotherapy when multiple sclerotic lesions are present is less satisfying. In contrast to patients with typical multiple myeloma, those with osteosclerotic myeloma are younger, present more often with peripheral neuropathy, have bone pain less frequently, have a more indolent course, and have involvement of lymph nodes and the spleen more frequently. The M components are small and with few exceptions contain lambda light chains. Bone lesions can be sclerotic, mixed sclerotic and lytic, or cystic with a rim of sclerosis. They are either solitary or multiple; when multiple, the number of lesions is usually limited. The extremities and the skull are spared, and examination of the bone marrow usually does not show multiple myeloma. A skeletal survey in this patient showed no sclerotic lesions; therefore, I must look elsewhere for the underlying diagnosis.

Most of the patients with the POEMS syndrome described by Nakanishi et al. had histologic changes in the lymph nodes resembling those of Castleman's disease, also known as 'angiofollicular lymph-node hyperplasia,' 'benign giant lymphoma,' and 'angiomatosus lymphoid hamartoma.' The lesions are most common in the mediastinum but are also found in other areas. Two types have been described — the hyaline vascular type and the plasma-cell type. In the early cases the lesions were solitary, but cases with multicentric lesions have been reported subsequently. The plasma-cell variant of Castleman's disease is found more commonly in the abdomen and may be associated with systemic symptoms and a variety of laboratory abnormalities. The plasma-cell proliferation is typically polyclonal, but monoclonal plasma-cell components may develop. The pathological findings in some patients with the POEMS syndrome resemble those of multicentric Castleman's disease of the plasma-cell type. Similar pathological findings have been seen in patients with human immunodeficiency virus infection and in patients in whom non-Hodgkin's lymphoma, plasmacytoma, and Kaposis's sarcoma subsequently developed. These patients and patients with the POEMS syndrome may have a disorder similar to but not identical with Castleman's disease. Therefore, I shall refer to the suspected pathological findings in this patient as multicentric angiofollicular lymph-node hyperplasia of the plasma-cell type.

Multicentric angiofollicular lymph-node hyperplasia of the plasma-cell type and osteosclerotic myeloma are both associated with the POEMS syndrome, and
both have been seen in the same patient. How are these entities related, and why do they behave differently from ordinary myeloma? Frizzera postulated that both these entities are disorders of lymph-node-bound lymphocytes, in contrast to bone marrow-associated and mucosa-associated lymphocytes. This theory explains why osteosclerotic myeloma frequently involves the lymph nodes and the spleen.

My final diagnosis is the POEMS syndrome, possibly associated with multicentric angiofollicular lymph-node hyperplasia of the plasma-cell type. The laboratory test reported was probably an immunoelectrophoresis that revealed the presence of a monoclonal protein. The odds slightly favor an IgG over IgA; about 90 percent of patients with the POEMS syndrome have lambda light chains.

CLINICAL DIAGNOSIS

POEMS syndrome.

DR. DAVID STEINBERG'S DIAGNOSIS

POEMS syndrome, possibly associated with multicentric angiofollicular lymph-node hyperplasia of plasma-cell type.

PATHOLOGICAL DISCUSSION

DR. NANCY L. HARRIS: Dr. Bloch will discuss the results of the diagnostic tests.

DR. KURT J. BLOCH: On immunoelectrophoresis of serum the IgG and IgA precipitin arcs were abnormal; the IgM arc was normal. The concentrations of the immunoglobulins were as follows: IgG 1080 mg, IgA 254 mg, and IgM 264 mg per 100 ml. Agarose-gel electrophoresis showed three low-concentration abnormal bands; on immunofixation these were identified as an IgA lambda protein, an IgG lambda protein, and an IgG kappa protein. These findings support the diagnosis of the POEMS syndrome in this patient.

Figure 2. Axillary Lymph-Node-Biopsy Specimen (×240). A small follicle contains concentric whorls of lymphoid cells and a penetrating blood vessel (arrows) typical of angiofollicular hyperplasia (Castleman's disease).

Figure 3. Axillary Lymph-Node-Biopsy Specimen (×65). In this area there is a monotonous follicular proliferation suggestive of follicular lymphoma.

Figure 4. Atypical Follicle with a Hyalinized Center (×160). This follicle is similar to the hyaline vascular follicles but is surrounded by a broad zone of atypical lymphoid cells.

DR. HARRIS: After receipt of the immunoelectrophoretic findings confirming the diagnosis of the POEMS syndrome, an axillary lymph-node biopsy was performed. Microscopical examination showed unusual features that defined a precise diagnosis. Portions of the lymph node showed a peculiar follicular hyperplasia, with lymphoid follicles of varying size, most of which had reactive germinal centers and broad mantle zones. Some of these follicles were hylalinized with concentric whorls of lymphoid cells consistent with Castleman's disease (Fig. 2). In other areas of the node there were large, closely packed follicles that replaced the nodal architecture, suggesting a follicular lymphoma (Fig. 3). However, some of these follicles also contained small hyaline vascular centers,
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reminiscent of angiofollicular hyperplasia (Fig. 4), and there was prominent vascular proliferation in the interfollicular region. In the centers of these large follicles the predominant cells were small cleaved follicular-center cells, with only small numbers of transformed cells, a finding very suggestive of a follicular lymphoma of predominantly small cleaved-cell type. In some follicles the mantle zone was replaced by an atypical proliferation identical to that in the follicle center (Fig. 5). The interfollicular region contained numerous small blood vessels, predominantly small lymphocytes, with no evidence of an increased number of plasma cells.

Immunoperoxidase stains showed that the follicles contained predominantly B cells, but with stains for immunoglobulin there was no evidence of a monoclonal B-cell population, either lymphocytic or plasmacytoid. The atypical follicles appeared to be immunoglobulin-negative, with surrounding mantle zones of polyclonal B cells; this is an abnormal phenotype but is not in and of itself diagnostic of lymphoma. Tissue was analyzed for evidence of immunoglobulin heavy-chain gene rearrangement, with the use of the Southern blot technique, and no clonal rearranged band could be detected.

In summary, this is a very unusual lymphoid proliferation, which has some morphologic features suggestive of Castleman’s disease of the hyaline-vascular type and other features suggestive of a follicular lymphoma.

The diagnosis of the POEMS syndrome is a clinical and immunologic one, based on the typical clinical features and the presence of an M component. As Dr. Steinberg has suggested, the histopathologic pattern is variable and ranges from osteosclerotic myeloma to the plasma-cell variant of Castleman’s disease, with a

number of reported cases showing simply lymphoid hyperplasia.20,21

Dr. Kadison, do you have follow-up information on this patient?

Dr. Paula Kadison: Because of the histopathologic diagnosis suggestive of malignant lymphoma the patient was treated with low doses of an alkylating agent. After three months of therapy with chlorambucil and continuation of prednisone there has been little improvement in her symptoms.

Anatomical Diagnoses

* Syndrome of polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes (POEMS).
* Atypical lymphoid hyperplasia with some features of angiofollicular hyperplasia, suggestive of follicular lymphoma.

References


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