Dr. Jason E. Faris (Medicine): A 66-year-old woman was admitted to this hospital because of cardiac and renal failure.

The patient had been well until approximately 6 months earlier, when dyspnea on exertion and leg edema developed. A diagnosis of congestive heart failure was made at another facility. Two months before this evaluation, dyspnea worsened. The patient was admitted to the other hospital. An electrocardiogram (ECG) showed T-wave inversions in leads I and aVL. The serum level of urea nitrogen was 38 mg per deciliter (13.6 mmol per liter), and the level of creatinine was 1.9 mg per deciliter (168 µmol per liter); the estimated glomerular filtration rate was 27 ml per minute per 1.73 m² of body-surface area. Results of a complete blood count and of tests of coagulation were normal, as were serum levels of sodium, carbon dioxide, glucose, total bilirubin, aminotransferases, and amylase. A chest radiograph was reportedly normal; computed tomography (CT) of the chest after the administration of contrast material reportedly revealed findings that were consistent with pulmonary edema. Noninvasive testing for venous thrombosis and pulmonary emboli was negative. Urinalysis at that time reportedly revealed protein (30 to 100 mg per deciliter), and a culture grew group B streptococci. Ultrasonography of the kidneys was normal. Diuretic agents were administered, and the patient was discharged.

Dyspnea on exertion persisted and gradually worsened.

Five days before admission, the patient came to the emergency department at this hospital. On examination, the temperature was 36.6°C, the blood pressure 143/80 mm Hg, the pulse 60 beats per minute, and the respiratory rate 18 breaths per minute. There was mild pitting edema in the legs, and the remainder of the examination was normal. Urinalysis at that time reportedly revealed protein (30 to 100 mg per deciliter), and a culture grew group B streptococci. Ultrasonography of the kidneys was normal. Diuretic agents were administered, and the patient was discharged.

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Dyspnea on exertion persisted and gradually worsened.
Table 1. Laboratory Data.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults†</th>
<th>5 Days before Admission</th>
<th>Hospital Days 1–4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea nitrogen (mg/dl)</td>
<td>8–25</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.60–1.50</td>
<td>3.10</td>
<td>3.49</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml/min/1.73 m²)</td>
<td>Abnormal if &lt;60</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>30–100</td>
<td>189</td>
<td></td>
</tr>
<tr>
<td>β₂-Microglobulin (mg/liter)</td>
<td>0.70–1.80</td>
<td>16.30</td>
<td></td>
</tr>
<tr>
<td>γ-Glutamyltransferase (U/liter)</td>
<td>5–36</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>N-terminal pro–brain natriuretic peptide (pg/ml)</td>
<td>0–900 (age 50–75 yr)</td>
<td>40,457</td>
<td>56,906</td>
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<tr>
<td>IgG (mg/dl)</td>
<td>614–1295</td>
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<tr>
<td>IgA (mg/dl)</td>
<td>69–309</td>
<td>43</td>
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</tr>
<tr>
<td>IgM (mg/dl)</td>
<td>53–334</td>
<td>17</td>
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</tr>
<tr>
<td>Free kappa light chain (mg/liter)</td>
<td>3.3–19.4</td>
<td>2760.0</td>
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</tr>
<tr>
<td>Free lambda light chain (mg/liter)</td>
<td>5.7–26.3</td>
<td>21.9</td>
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<tr>
<td>Ratio of free kappa to free lambda light chains</td>
<td>0.3–1.7</td>
<td>126.0</td>
<td></td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea nitrogen (mg/dl)</td>
<td>Not defined</td>
<td>353</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/ml)</td>
<td>Not defined</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Microalbumin (mg/dl)</td>
<td>0.0–2.0</td>
<td>202.5</td>
<td></td>
</tr>
<tr>
<td>Ratio of microalbumin to creatinine (mg/g of creatinine)</td>
<td>&lt;30.0</td>
<td>4500.0</td>
<td></td>
</tr>
</tbody>
</table>

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for β₂-microglobulin to nanomoles per liter, multiply by 84.75.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

oped, with rhinorrhea, worsening orthopnea, and dyspnea on exertion, and the patient was able to walk only short distances before resting. She returned to the emergency department.

The patient reported no chest pain or pressure and no nausea, sore throat, rashes, myalgias, hemoptysis, sinusitis, vomiting, diarrhea, abdominal pain, fevers, chills, or dysuria. She had hypertension, hyperlipidemia, osteoarthritis, coronary artery disease, and a history of myocardial infarction several years earlier. She was born in Europe, had immigrated to the United States 40 years earlier, lived with her husband, and was retired. She did not smoke, drink alcohol, or use illicit drugs. Medications included furosemide, ezetimibe, atenolol, pravastatin, valsartan, and acetylsalicylic acid. Her father had had a myocardial infarction at 76 years of age, and her brother had had a stroke at 45 years of age.

On examination, the temperature was 38.3°C, the blood pressure 164/94 mm Hg, the pulse 83 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 93% while the patient was breathing ambient air. The jugular veins were distended 11 cm above the right atrium; there were decreased lung sounds with expiratory wheezes bilaterally and crackles at the left base. A grade 2/6 systolic murmur was heard at the left upper sternal border and apex; there were decreased lung sounds with expiratory wheezes bilaterally and crackles at the left base. A grade 2/6 systolic murmur was heard at the left upper sternal border and apex; there were decreased lung sounds with expiratory wheezes bilaterally and crackles at the left base. A grade 2/6 systolic murmur was heard at the left upper sternal border and apex; there were decreased lung sounds with expiratory wheezes bilaterally and crackles at the left base.
The complete blood count and differential count were normal, as were antistreptolysin O and anti-DNase B titers and measurements of electrolytes, glucose, calcium, phosphorus, magnesium, total protein, albumin, globulin, total and direct bilirubin, aminotransferases, complement (C3 and C4), iron, iron-binding capacity, and ferritin; tests for hepatitis B and C viruses were negative. Screening for toxins and serologic testing for the human immunodeficiency virus, syphilis, and cryoglobulins were negative; a test for antinuclear antibodies was positive at 1:40 and 1:160 dilutions, in a speckled pattern; antibodies to double-stranded DNA, Ro, La, Sm, RNP, Scl-70, and histone were negative. Urinalysis showed clear, yellow urine, with a specific gravity of 1.012, pH 6.5, 2+ occult blood, 3+ albumin, 20 to 50 red cells, a few squamous cells per high-power field, and 10 to 20 hyaline casts per low-power field. Cultures of the sputum grew normal respiratory flora; the urine grew moderate mixed flora. Testing for influenza A and B viruses and respiratory syncytial virus antigens was negative. Other test results are shown in Table 1.

Furosemide and levofloxacin were administered, and the patient was admitted to this hospital. The next day, the temperature was normal and bibasilar pulmonary crackles persisted. CT of the chest revealed atelectasis in the lingula, patchy ground-glass opacities in the right upper lobe, and diffuse bronchial-wall and interlobular septal thickening, features that are consistent with pulmonary edema or atypical pneumonia. The pulmonary artery was mildly enlarged, and multiple subcentimeter lymph nodes in the mediastinum and diffuse osteopenia were present. A transthoracic echocardiogram showed an ejection fraction of 56% with biventricular hypertrophy, left atrial dilatation (55 mm in the greatest dimension), elevated left atrial pressure, a left ventricular hypertrophy with septal predominance, and normal left ventricular systolic function (Fig. 1A and 1B). The right ventricle was also hypertrophied, and there was mild thickening of both the mitral and the tricuspid valves (Fig. 1B and 1C). Granular speckling of the ventricular walls was not visualized, and there was no pericardial effusion. The combination of ventricular hypertrophy, normal systolic function, and marked atrial enlargement in a nondilated heart was suggestive of an infiltrative cardiomyopathy.

Dr. Raje: Our patient presented with two major problems: cardiac and renal failure. The B-type natriuretic peptide (BNP) level was elevated, and an ECG showed a low-voltage pattern. The echocardiogram showed findings suggestive of infiltrative cardiomyopathy.

The patient also had acute renal failure with proteinuria. An extensive laboratory evaluation revealed decreased serum immunoglobulin levels, elevated free kappa light-chain levels, and an abnormal ratio of free kappa to free lambda light chains. The presence of elevated kappa light-chain levels was suggestive of a diagnosis of plasma-cell myeloma and prompted us to perform a radiographic skeletal survey.

Dr. Tara M. Lawrimore: A skeletal survey revealed generalized osteopenia and scattered small, discrete osteolytic lesions in the skull and much more conspicuously in both humeri (Fig. 2). The most likely cause of these findings is a malignant tumor; the appearance is characteristic of multiple myeloma. On occasion, osseous metastases from primary cancers that have a propensity to produce lytic lesions, such as thyroid cancer, might have a similar presentation, but these are encountered infrequently.

Dr. Raje: The presence of increased serum free kappa light chains and lytic bone disease on a skeletal survey raises suspicion for multiple myeloma. In addition, the presence of cardiac failure...
and ultrasonographic findings that were consistent with an infiltrative cardiomyopathy are suggestive of amyloidosis, a condition associated with multiple myeloma. Renal failure could be due to multiple myeloma as well, with either cast nephropathy or amyloidosis or both. The diagnostic procedures were bone marrow aspiration and biopsy and abdominal fat-pad biopsy.

**DR. NOOPUR S. RAJE’S DIAGNOSIS**

Multiple myeloma with AL amyloidosis involving the heart and kidneys.

**PATHOLOGICAL DISCUSSION**

*Dr. Aliyah R. Sohani:* The core-biopsy specimen of the bone marrow contained increased plasma cells both singly and in conspicuous clusters. According to a bone-marrow–aspirate count, 17% of the cells were plasma cells, which were kappa light chain–restricted according to in situ hybridization for mRNA and flow cytometry (Fig. 3A through 3D). Cytogenetic analysis of the bone marrow revealed a normal female karyotype in 20 cells in metaphase; examination of additional cells by fluorescence in situ hybridization (FISH) showed the presence of monosomy 13, trisomy 4, and trisomy 11. These findings are diagnostic of a plasma-cell neoplasm.

Categories of plasma-cell neoplasms include monoclonal gammopathy of undetermined significance (MGUS), asymptomatic plasma-cell myeloma, symptomatic plasma-cell myeloma, solitary plasmacytoma, and immunoglobulin deposition diseases including AL amyloidosis (also called primary amyloidosis). These conditions have different prognoses and are managed differently. Further classification of this patient’s condition requires correlation with clinical and radiologic findings and results of other laboratory and pathology studies.

Serum protein electrophoresis demonstrated abnormal banding, with markedly decreased normal immunoglobulin (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Serum kappa Bence Jones protein was suspected on immunofixation and confirmed by nephelometry, immunodiffusion, and immunoelectrophoresis (Fig. 1 in the Supplementary Appendix). Congo red staining of the fine-needle aspirate of the fat pad emitted a characteristic apple-green birefringence under polarized light (Fig. 3E and 3F), which confirmed the secretion of an amyloidogenic light chain by the...
plasma-cell neoplasm and amyloid deposition in tissues.

In summary, this patient has a plasma-cell neoplasm characterized by clonal plasma cells in the bone marrow, no M protein, monoclonal serum free light chains, Bence Jones proteinuria, lytic bone lesions, and amyloidosis.

Does this patient have plasma-cell myeloma, AL amyloidosis, or both? Plasma-cell neoplasms have proved challenging to classify in a biologically correct and clinically useful way. Since the immunoglobulin products of plasma cells can be detected in the serum and urine, evidence of small clones of plasma cells may be detected by routine laboratory tests in healthy patients in whom symptoms that require treatment may never develop. Thus, the definition of plasma-cell myeloma has rested on identifying clinical and laboratory features that predict when the burden of plasma cells has accumulated to such a degree that the patient requires treatment. According to current guidelines of the International Myeloma Working Group and the World Health Organization, the diagnosis of plasma-cell myeloma, in the absence of myeloma-related end-organ damage (i.e., hypercalcemia, renal failure, anemia, or bone lesions), requires the presence of a serum M-protein level of at least 30 g per liter or at least 10% clonal plasma cells in the bone marrow, so-called asymptomatic myeloma. In contrast, if myeloma-related end-organ damage is present, the diagnosis of plasma-cell myeloma requires only the presence of an M protein in the serum or urine in any amount and any number of clonal plasma cells in the bone marrow (usually exceeding 10% of all cells). This patient has lytic bone lesions and bone marrow consisting of more than 10% plasma cells, so her disease meets the criteria for plasma-cell myeloma.

Amyloidosis, which this patient also has, occurs when the secreted immunoglobulin light chain forms beta-pleated sheets that are deposited in tissues, leading to organ damage. AL amyloidosis is always the result of a clonal plasma-cell neoplasm, but symptoms due to amyloid deposition usually develop at a time when the plasma-cell burden is low — in most cases, the bone marrow consists of less than 10% plasma cells, with low levels of M protein (<30 g per liter), similar to the levels seen in MGUS. If the patient’s symptoms are entirely attributable to organ damage from amyloid deposition, the resulting organ failure does not constitute a criterion for the diagnosis of plasma-cell myeloma. However, amyloidosis also occurs in up to 10% of patients with overt plasma-cell myeloma.

The findings in this patient are diagnostic of plasma-cell myeloma with associated AL amyloidosis.

**DISCUSSION OF MANAGEMENT**

Dr. Raje: On the basis of the International Myeloma Working Group criteria, a diagnosis of symptomatic multiple myeloma with amyloidosis was made in this patient. In determining treatment, we need...
Figure 3. Results of Bone Marrow and Abdominal Fat-Pad Studies.

A smear of the bone marrow aspirate (Panel A, Wright–Giemsa) shows increased numbers of plasma cells (arrows), constituting 17% of the total nucleated cells. In the core-biopsy specimen (Panel B, hematoxylin and eosin), plasma cells form conspicuous clusters (oval) and have atypical features, including irregular nuclear contours and small, prominent eosinophilic nucleoli. Plasma cells stained strongly for CD138 (Panel C), and they expressed monotypic kappa light chain (Panel D, in situ hybridization for kappa immunoglobulin light-chain messenger RNA [mRNA]); very few lambda-positive plasma cells were present (Panel D, inset, in situ hybridization for lambda immunoglobulin light-chain mRNA). Flow cytometry revealed concordant findings with a small CD38-positive, CD138-positive, CD19-negative kappa light-chain–restricted plasma-cell population that was identified (not shown). Congo red staining of a biopsy specimen of a fat pad, obtained by fine-needle aspiration, is positive, with diffuse red staining (Panel E). Under polarized light microscopy, apple-green birefringence that is characteristic of amyloid is seen (Panel F, Congo red stain, polarized light).
to assess the stage of the disease and the prognostic risk factors and address the associated medical problems, such as renal and cardiac failure.

PROGNOSTIC FACTORS IN PLASMA-CELL MYELOMA

There are three stages of multiple myeloma. The stages are defined on the basis of the serum levels of albumin and β2-microglobulin (Table 2), and the prognosis with conventional therapies differs substantially according to the stage. This patient’s serum β2-microglobulin level was more than 5.5 mg per liter; therefore, according to the International Staging System, she has stage III myeloma. Cytogenetic findings also affect prognosis (Table 2). This patient had hyperdiploidy and deletion 13 detected by FISH but not detected by metaphase analysis. The presence of deletion 13 on metaphase analysis and the absence of a hyperdiploid state are considered poor prognostic features in the context of conventional chemotherapy; this patient did not have either.

This patient also has AL amyloidosis. AL amyloidosis is associated with organ damage, which may dominate the clinical picture. Cardiac involvement, seen in 30% of patients with AL amyloidosis, is associated with a restrictive cardiomyopathy, which presents with signs and symptoms similar to those in this patient, including rapidly progressive heart failure, a low-voltage pattern on ECG, increased mean left ventricular wall thickness in the absence of hypertension or other causes of left ventricular hypertrophy, and a preserved or only slightly decreased ejection fraction. Liver function abnormalities may occur as a result of right heart failure or amyloid infiltration of the liver. Elevation of alkaline phosphatase levels and normal or only mild elevation of aminotransferases, as noted in this patient, occur as a consequence of sinusoidal infiltration by amyloid. Involvement of other organs may be seen, such as the gastrointestinal tract (in 7% of patients) and soft tissue (in 3%), as well as nervous system involvement causing peripheral autonomic neuropathy (in 5%); this patient does not appear to have any of these complications. Renal involvement is seen in 46% of patients with amyloidosis but is also common in myeloma without amyloidosis.

RENAL MANIFESTATIONS OF PLASMA-CELL MYELOMA

Dr. David J. R. Steele: This patient with multiple myeloma had kidney failure that developed over a period of 6 months, associated with nephrotic-range proteinuria, and worsened in the weeks before admission. The kidney failure is most likely a complication of multiple myeloma, which is an epidemiologically important cause of kidney failure, affecting nearly 8000 patients per year in the United States. The manifestations of renal disease associated with myeloma include proximal and distal tubular dysfunction due to cellular injury from filtered light chains, myeloma cast nephropathy, amyloidosis, deposition disease with light chains or heavy and light chains, cryoglobulinemia, interstitial plasma-cell infiltration, and on rare occasions, proliferative glomerulonephritis and interstitial nephritis.

Cast nephropathy accounts for 40 to 60% of cases of myeloma-associated renal failure and may cause acute renal failure, as seen in this patient. It is due to the overloading of renal mechanisms for light-chain reabsorption and the properties of light chains excreted in the urine. In the distal nephron, light chains interact with the Tamm–Horsfall protein and albumin, forming casts, which are deposited in the distal and collecting tubules, causing dilatation and atrophy. This patient had casts in her urine sediment and acute renal failure, both of which could be caused by cast nephropathy. However, nephrotic-range proteinuria is not usually seen in cast nephropathy.

This patient also had AL amyloidosis, which may be affecting her kidneys; deposits may occur in the renal glomerular basement membrane, mesangium, and peritubular tissues. Thirty percent of patients with renal amyloidosis have the nephrotic syndrome, and 20% have a serum creatinine level greater than 2 mg per deciliter at presentation, similar to this patient. However, renal failure requiring dialysis occurs in less than 5% of patients with renal amyloidosis.

SUMMARY

In this patient with nephrotic-range proteinuria, an accelerated decline in renal function, and a high concentration of serum kappa free light chains, our clinical diagnosis was renal amyloidosis, complicated by myeloma cast nephropathy. Since she was acutely ill and at risk for complications, a renal biopsy was not performed.
There are two categories of stage II myeloma. In one category, the serum β₂-microglobulin level, <3.5 mg per liter, and serum albumin level, >3.5 g per deciliter; median survival, 62 months. In the second category, the serum β₂-microglobulin level is at least 3.5 mg per liter and less than 5.5 mg per liter; serum albumin level is less than 3.5 g per deciliter and the serum albumin level, >3.5 g per deciliter; median survival, 44 months. In the second category, the serum β₂-microglobulin level is at least 3.5 mg per liter and less than 5.5 mg per liter; serum albumin level is less than 3.5 g per deciliter and the serum albumin level, >3.5 g per deciliter; median survival, 29 months.

### Table 2. Prognostic Factors in Plasma-Cell Myeloma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Serum β₂-microglobulin level, &lt;3.5 mg per liter, and serum albumin level, &gt;3.5 g per deciliter; median survival, 62 months</td>
</tr>
<tr>
<td>II†</td>
<td>Not stage I or III; median survival, 44 months</td>
</tr>
<tr>
<td>III</td>
<td>Serum β₂-microglobulin level, &gt;5.5 mg per liter; median survival, 29 months</td>
</tr>
<tr>
<td>Cytogenetic features</td>
<td></td>
</tr>
<tr>
<td>Unfavorable risk</td>
<td>Deletion 13 or aneuploidy according to metaphase analysis</td>
</tr>
<tr>
<td></td>
<td>t(4;14) or t(14;16) according to FISH</td>
</tr>
<tr>
<td></td>
<td>Deletion 17p13 according to FISH</td>
</tr>
<tr>
<td></td>
<td>Hypodiploidy</td>
</tr>
<tr>
<td>Favorable risk</td>
<td>Absence of the features associated with unfavorable risk</td>
</tr>
</tbody>
</table>

* Data are from Greipp et al., Stewart et al., and Munshi et al. FISH denotes fluorescence in situ hybridization.

† There are two categories of stage II myeloma. In one category, the serum β₂-microglobulin level is less than 3.5 mg per liter and the serum albumin level is less than 3.5 g per deciliter. In the second category, the serum β₂-microglobulin level is at least 3.5 mg per liter and less than 5.5 mg per liter, regardless of the serum albumin level.

We initiated hemodialysis for this patient to treat her congestive heart failure and uremia. She had rapid improvement in her dyspnea and edema. We did not use plasmapheresis.

### Treatment of Plasma-Cell Myeloma

**Dr. Raje:** Management of multiple myeloma has evolved in the past decade so that there are several options for this patient. The introduction of proteasome inhibitors, such as bortezomib, and immunomodulatory drugs, such as thalidomide and lenalidomide, has resulted in improvement in the overall survival rate of patients with myeloma. Five drug combinations are currently approved for the treatment of newly diagnosed myeloma and relapsed myeloma. These new agents have markedly affected the outcome of patients such as this one who had renal failure and in whom older chemotherapy regimens elicited a poor response. In a series of patients with myeloma-related renal failure treated with dexamethasone in combination with thalidomide, bortezomib, or both, renal failure was reversed in 80% of the patients in a median of 0.8 months.

In addition to myeloma-related renal failure, this patient has amyloidosis that is contributing to her renal disease and causing cardiac failure. Standard therapy for amyloidosis has been high-dose chemotherapy with autologous stem-cell rescue, in those who could tolerate such treatment. In a retrospective study of the use of bortezomib in patients with newly diagnosed or previously....
treated amyloidosis, the rate of the overall hematologic response (i.e., the reduction of the level of abnormal serum free light chains or evidence of bone marrow involvement by clonal plasma cells) was 71%, with 30% of patients having a response in at least one affected organ.23

How does renal failure affect the administration of these drugs? Adjustment of the dose of bortezomib is not required because clearance is independent of renal function. However, since dialysis may reduce the level of bortezomib in the blood, the drug should be administered after the dialysis procedure. Adverse events associated with thalidomide are not affected by renal failure, but there is a risk of severe thalidomide-associated hyperkalemia among patients receiving dialysis. Although the rate of clearance of thalidomide is doubled during dialysis, the dose does not need to be changed in patients receiving dialysis. Lenalidomide, however, is excreted by the kidneys; careful dose adjustment is required in patients with renal failure, and close observation of blood counts is required for minimizing the potential for hematologic toxicity.24

This patient was treated with bortezomib and dexamethasone on a twice-weekly schedule. The treatment course was complicated by grade 2 painful neuropathy (on a scale of 0 to 4, with 4 indicating the most severe neuropathy) during cycle 5, after which the patient was switched to weekly bortezomib, with excellent tolerance, for three additional 5-week cycles. Three months after she started treatment, the creatinine clearance remained less than 10 ml per minute. At 4 months, it increased into the range of 10 to 20 ml per minute. At 5 months, the patient was able to discontinue dialysis. Currently, the creatinine level is 1.9 mg per deciliter and the urinary protein level has returned to normal.

What additional therapy could be considered for this patient? Some patients with AL amyloidosis have undergone organ transplantation (e.g., sequential heart and peripheral stem-cell transplantation).27 This patient was not eligible for high-dose therapy or organ transplantation because she had involvement of two organs.

After bortezomib-based therapy, this patient had a complete hematologic response and became hemodialysis-independent. At the present time, she is receiving no treatment, and complete remission has been sustained for more than 2 years since the diagnosis.

Dr. Nancy Lee Harris (Pathology): Are there any questions?

Dr. Bruce Chabner (Hematology–Oncology): In a patient with normal renal function, would you recommend a combination of bortezomib and lenalidomide as a primary therapy for myeloma? What is the combination of choice?

Dr. Raje: The combination of bortezomib and dexamethasone is generally the standard in myeloma-related acute renal failure, because it decreases the tumor burden very rapidly and the dosing is not affected by the presence of renal failure. Combination treatments are routinely used in patients who do not have renal failure. A recent phase 1 and phase 2 trial combining lenalidomide with bortezomib and dexamethasone showed a 100% overall response rate with few adverse effects.28 A phase 3 Eastern Cooperative Oncology Group trial is now in progress (ClinicalTrials.gov number, NCT00522392) to assess the benefit of this combination as compared with bortezomib and dexamethasone alone.

**ANATOMICAL DIAGNOSIS**

Plasma-cell myeloma with AL amyloidosis involving the heart and kidneys.

This case was discussed at the Massachusetts General Hospital Cancer Center Grand Rounds.

Dr. Raje reports receiving consulting fees from Celgene, Novartis, and Amgen and grant support from AstraZeneca and Acetylon. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Mandakolathur Murali for providing the images in Figure 1 in the Supplementary Appendix.

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3. Criteria for the classification of monoclonal gammopathies, multiple myeloma
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