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Case 27-2015: A 78-Year-Old Man with Hypercalcemia and Renal Failure

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PRESENTATION OF CASE

Dr. Sahir Kalim (Medicine): A 78-year-old man was admitted to this hospital because of hypercalcemia and renal failure.

The patient had been in his usual health until approximately 4 months before the current admission; he had been admitted to this hospital then because of dyspnea, cough, rib pain, flank pain, and one episode of hematuria that had reportedly occurred 1 week earlier. On examination, the vital signs were normal; there were rales in the bases of both lungs and a systolic ejection murmur (grade 2/6). Urinalysis showed no evidence of blood.

Dr. P. Gabriel Peterson: Imaging studies that were performed during that hospitalization included chest radiography and computed tomographic (CT) angiography of the chest, abdomen, and pelvis. These studies revealed basilar atelectasis, changes consistent with mild congestive heart failure, and a new subpleural nodular opacity (1.3 cm in diameter) in the right middle lobe (Fig. 1A). There was also bilateral mediastinal and hilar lymphadenopathy with coarse calcifications, a finding that was unchanged from imaging studies that had been obtained 2 years earlier (Fig. 1B).

Dr. Kalim: During that admission, the patient's cough, dyspnea, and flank pain improved with supportive care. At discharge, recommendations included outpatient follow-up with CT of the chest, cytologic examination of a urine specimen, and possible cystoscopy.

Four months later, on the day of the current admission, the patient was seen in a clinic affiliated with this hospital for a follow-up visit. He reported that two episodes of hematuria had occurred during the previous 2 months, with fatigue but no fevers, chills, numbness, headache, neck stiffness, difficulty swallowing, incontinence, trauma, or infection. He had hypertension, hyperlipidemia, benign prostatic hypertrophy, mild cognitive decline, and choreiform movements. He had undergone aortic-valve replacement and repair of an aortic aneurysm 2 years earlier; he had had a positive tuberculin skin test with a reportedly negative evaluation 6 years earlier. His medications included donepezil hydrochloride, citalopram, tamsulosin, ranitidine, quetiapine, aspirin, psyllium, and a multivitamin. He had no known allergies. He was born in Europe and had lived in South America for

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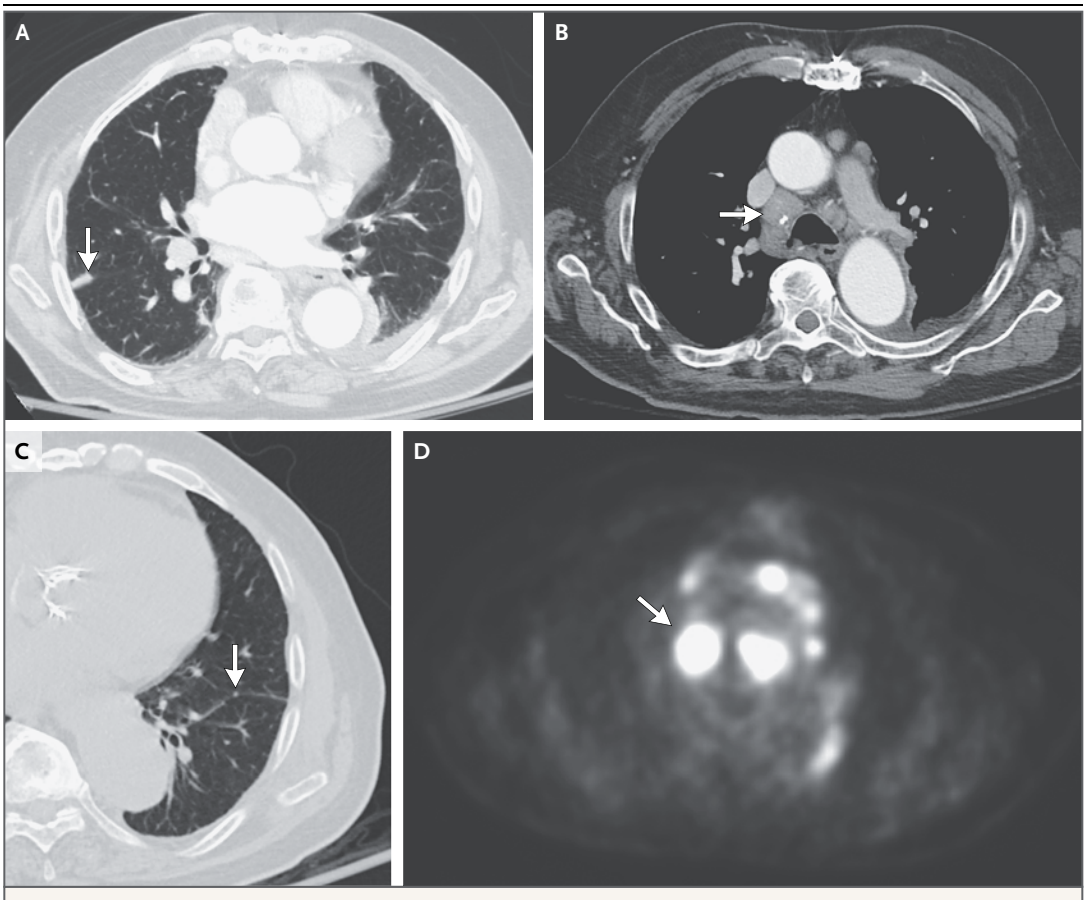

Figure 1. Imaging Studies of the Chest.

CT scans of the chest that were obtained 4 months before the current admission (Panels A and B) show a new nodular lesion in the right middle lobe along the major fissure (Panel A, arrow), as well as bilateral mediastinal and hilar lymphadenopathy with coarse calcifications, a finding that was unchanged from imaging studies that had been obtained 2 years earlier (Panel B, arrow). A CT scan of the chest that was obtained on admission (Panel C) shows multiple small pulmonary nodules, findings that were unchanged from imaging studies that had been obtained 2 years earlier (arrow). One month later, an ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography scan (Panel D), which was obtained at the level of the carina, shows marked FDG avidity throughout the bilateral mediastinal and hilar lymphadenopathy (arrow).

10 years; he had immigrated to the United States when he was in his 40s. He lived with his wife and was retired after working in the construction and food industries. He maintained a low-salt and low-cholesterol diet, had stopped smoking 30 years earlier, had stopped drinking alcohol 1 month earlier, and did not use illicit drugs. His father had had asthma and a myocardial infarction at 62 years of age, his mother had had heart failure in her 70s, a brother had had a stroke in his 80s, and his son had died in his 30s because of arrhythmia and cardiomyopathy; his other children were healthy.

On examination, the blood pressure was 108/66 mm Hg, and the pulse 68 beats per minute. The first and second heart sounds were normal; a systolic murmur, grade 1/6, was heard at the left base. The remainder of the examination was unchanged from baseline. The platelet count and red-cell indexes were normal, as were blood levels of glucose, total protein, albumin, globulin, total and direct bilirubin, aspartate aminotransferase, and alanine aminotransferase; other laboratory test results are shown in Table 1. Urinalysis revealed clear yellow urine, with a specific gravity of 1.009, a pH of 5.5, and trace albumin by dipstick, and was otherwise normal. After the test results were known, the patient

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	4 Hr before Admission, Clinic	On Admission	21 Days after Admission, Clinic	6 Wk after Admission, On Readmission
Blood					
Hematocrit (%)	41.0–53.0	29.6	31.5	27.7	24.3
Hemoglobin (g/dl)	13.5–17.5	10.5	11.4	9.5	8.7
White-cell count (per mm^3)	4500–11,000	4600	5100	3400	4000
Differential count (%)					
Neutrophils	40–70	63	68	58	61
Lymphocytes	22–44	18	15	25	25
Monocytes	4–11	14	11	11	10
Eosinophils	0–8	4	5	5	4
Basophils	0–3	1	1	1	0
Reticulocytes (%)	0.5–2.5		1.4		
Erythrocyte sedimentation rate (mm/hr)	0–11		56	79	
Sodium (mmol/liter)	135–145	138	136	137	140
Potassium (mmol/liter)	3.4–4.8	4.9	4.7	4.3	4.9
Chloride (mmol/liter)	100–108	98	97	103	104
Carbon dioxide (mmol/liter)	23.0–31.9	28.4	29.2	23.5	24.4
Urea nitrogen (mg/dl)	8–25	77	75	53	69
Creatinine (mg/dl)	0.60–1.50	5.26	5.36	3.10	4.95
Estimated glomerular filtration rate (ml/min/1.73 m^2)	≥60	11	11	21	12
Calcium (mg/dl)	8.5–10.5	14.9	17.1	10.1	10.1
Phosphorus (mg/dl)	2.6–4.5		5.5		4.5
Magnesium (mg/dl)	1.7–2.4		3.0		2.3
Alkaline phosphatase (U/liter)	45–115	154		128	
γ-Glutamyltransferase (U/liter)	8–61		152		
Angiotensin-converting enzyme (U/liter)	7–46		61		
Parathyroid hormone (pg/ml)	10–60		22	31	27
Thyrotropin (μU/ml)	0.40–5.00			0.08	
25-Hydroxyvitamin D (ng/ml)	33–100		20		22

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Prostate-specific antigen (ng/ml)	0.0–4.0	5.1		
β_2-Microglobulin (mg/liter)	0.8–3.0	9.3	13.7	15.7
Immunoglobulins (mg/dl)				
IgA	69–309	179	208	188
IgG	614–1295	831	896	868
IgM	53–334	521	541	510
Serum protein electrophoresis and immunofixation		Abnormal pattern; 0.24 g/dl IgM kappa M component in the gamma region	Abnormal pattern; 0.22 g/dl band in the gamma region	Abnormal pattern; 0.20 g/dl band in the gamma region
Free kappa light chain (mg/liter)	3.3–19.4		27.0	31.5
Free lambda light chain (mg/liter)	5.7–26.3		30.4	34.7
Free kappa:free lambda ratio	0.3–1.7		0.9	0.9
Antinuclear antibody				Positive at 1:1280 dilution; fine-to-coarse speckling of the nuclei
Antibody to proliferating-cell nuclear antigen	Not present			Present
Urine				
Bence Jones protein (in 50× concentrated urine)	No Bence Jones protein present	Small amount of kappa Bence Jones protein present; trace albumin present		Small amount of kappa Bence Jones protein present; small amount of albumin, alpha, beta, and probably intact immunoglobulin; very low concentration of IgM kappa M component (same location as serum IgM kappa)
Free kappa light chain (mg/liter)	0.4–15.1			86.3
Free lambda light chain (mg/liter)	0.8–10.1			13.4
Free kappa:free lambda ratio	0.5–4.0			6.4

* 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 calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to millimoles per liter, multiply by 0.4114.

† 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.

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was advised to go the emergency department of this hospital.

In the emergency department, the patient reported diffuse nonradiating lower abdominal pain, which he rated at 4 on a scale of 0 to 10 (with 10 indicating the most severe pain). He also reported severe constipation, increasing urinary frequency over a period of 1 week, decreased oral intake, weakness and fatigue of 1 month's duration, and weight loss of 4.5 kg during the previous 3 months. He had no fevers, chills, night sweats, cough, hemoptysis, dyspnea, nausea, vomiting, diarrhea, rashes, chest pain, palpitations, syncope, or leg swelling.

On examination, the blood pressure was 149/65 mm Hg, the pulse 50 beats per minute, the temperature 36.4°C, the respiratory rate 18 breaths per minute, and the oxygen saturation 98% while the patient was breathing ambient air. The abdomen was soft and mildly tender in the lower quadrants, without rebound, and the remainder of the examination was unchanged. Blood levels of lactate dehydrogenase and vitamin A were normal, and testing was negative for hepatitis B virus surface antibodies and antigen and hepatitis C virus antibodies; additional laboratory test results are shown in Table 1. Repeat urinalysis revealed 1+ occult blood and albumin by dipstick; examination of the urinary sediment revealed 0 to 2 red cells and white cells, few bacteria, and few squamous cells per high-power field. The urinary sodium level was 55 mmol per liter, the creatinine level was 0.44 mg per milliliter (3890 μmol per liter), and the osmolality was 329 mOsm per kilogram of water. A chest radiograph revealed a tortuous calcified aorta, evidence of aortic-valve replacement, and no evidence of pneumonia or effusion. Electrocardiography (ECG) showed sinus rhythm at a rate of 50 beats per minute; the results were otherwise unchanged from earlier tracings. The patient was admitted to this hospital.

Normal saline was infused, and salmon calcitonin was administered. The calcium level decreased to 13.4 mg per deciliter (3.35 mmol per liter), at which time the ionized calcium level was 1.73 mmol per liter (6.92 mg per deciliter; reference range, 1.14 to 1.30 mmol per liter [4.56 to 5.20 mg per deciliter]). Two additional liters of saline were infused. On the second day, hemodialysis was performed, and the ionized calcium level decreased to 1.27 mmol per liter (5.08 mg per deciliter). The next day, pamidronate was administered.

Dr. Peterson: During the next 8 days, additional imaging studies were obtained. CT of the chest, performed without the administration of contrast material, revealed multiple small pulmonary nodules, many of which were subpleural (Fig. 1C). The nodules were unchanged from imaging studies obtained 2 years earlier, and the new nodule in the right middle lobe that had been seen on the previous study had resolved. CT of the abdomen and pelvis, performed without the administration of contrast material, revealed a right renal cyst (2.9 cm in diameter) and an enlarged prostate. A bone scan showed no evidence of bone metastases. Thyroid ultrasonography revealed bilateral colloid cysts but no extrathyroid nodules. A skeletal survey showed diffuse osteopenia, with lucent lesions in the calvarium and possibly the mandible, as well as subtle, indeterminate lucent lesions in the legs that raised concerns about multiple myeloma or metastatic cancer.

Dr. Kalim: Cytologic examination and culture of the urine were negative. On the sixth hospital day, testing for cryoproteins was negative. Pathological examination of a bone marrow–biopsy specimen showed 7% plasma cells and an increased number of monoclonal plasma cells with kappa light chains. The patient was discharged on the 11th hospital day; sodium bicarbonate was added to his previous medication regimen. Eleven days later (21 days after the current admission), at an outpatient visit, additional test results were obtained (Table 1).

Dr. Peterson: The next week, 1 month after the current admission, ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) revealed marked FDG avidity in the mediastinal and hilar lymphadenopathy (Fig. 1D).

Dr. Kalim: Two weeks later, the patient was readmitted to this hospital because of worsening renal failure. Levels of complement (C3 and C4) were normal, and testing was negative for antibodies to double-stranded DNA, SSA (Ro), SSB (La), Sm, and RNP; other laboratory test results are shown in Table 1. A renal biopsy was performed.

Dr. Eugene J. Mark: Pathological examination of the renal-biopsy specimen revealed two glomeruli with global sclerosis (out of the six examined), interstitial fibrosis, and tubular atrophy affecting 30% of the cortex. The principal finding was

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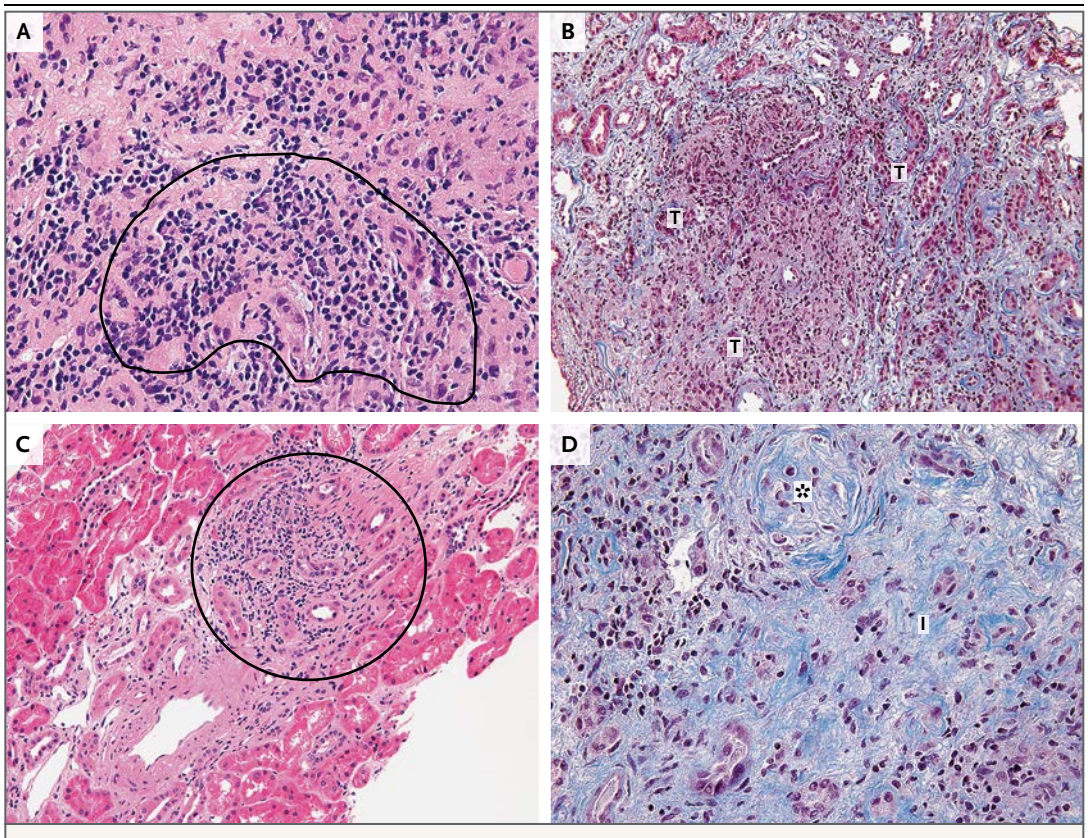

Figure 2. Renal-Biopsy Specimen.

Pathological examination of a renal-biopsy specimen was performed. Panel A (hematoxylin and eosin) shows foci in which the renal cortex is largely replaced with inflammation and fibrosis (some within the outline); the inflammation is lymphocytic and plasmacytic. Panel B (Masson trichrome) shows focal sclerosis (blue) and atrophic tubules (T) in areas of fibrosis. Panel C (hematoxylin and eosin) shows relatively discrete regions of granulomatous histiocytic inflammation and fibrosis (circle). Panel D (Masson trichrome) shows global sclerosis of glomeruli (asterisk) and interstitium (I) that is associated with inflammation.

a focal but dense infiltrate of mononuclear cells that was composed predominantly of lymphocytes, with some histiocytes and plasma cells and without eosinophils. There were foci of tubulitis that was characterized by disruption of basement membrane by the inflammatory cells (Fig. 2A). Interstitial fibrosis resulted in tubular atrophy (Fig. 2B). These findings indicate chronic active tubulointerstitial nephritis. In addition, localized collections of histiocytes were present. The epithelioid character of the histiocytes, as well as their circumscription, can be described as granulomatous or as poorly formed granulomas (Fig. 2C).[1] The glomeruli that were observed in the renal-biopsy specimen were normal apart from the global sclerosis in areas of inflammation (Fig. 2D).

Dr. Kalim: The patient was discharged on the fourth hospital day. Four weeks later, a diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Neil R. Powe: Multiple symptoms — including weakness, fatigue, bone pain, flank pain, hematuria, abdominal pain, anorexia, constipation, polyuria, and bradycardia — developed in this 78-year-old man over a period of several months. In retrospect, all these symptoms could have been attributed to hypercalcemia. In an attempt to arrive at the correct diagnosis, I will focus my differential diagnosis on disorders that cause hypercalcemia and renal failure. Causes of hypercalcemia can be divided into those that are parathyroid hormone (PTH)–dependent and those that are PTH-independent.

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PTH-DEPENDENT HYPERCALCEMIA

The most common cause of PTH-dependent hypercalcemia is primary hyperparathyroidism, which is frequently identified in patients with asymptomatic, mildly elevated serum calcium levels (usually <12 mg per deciliter [<3 mmol per liter]) and is often discovered incidentally on routine laboratory testing.[2] This patient's serum calcium level was 17.1 mg per deciliter (4.28 mmol per liter) on admission, which is much higher than the level typically associated with primary hyperparathyroidism.

Tertiary hyperparathyroidism is a condition that develops in patients with chronic end-stage renal disease. Chronic hyperphosphatemia, hypocalcemia, vitamin D deficiency, or inadequate production of 1,25-dihydroxyvitamin D causes persistent stimulation and production of PTH, resulting in parathyroid autonomy. This patient's history is not suggestive of tertiary hyperparathyroidism because the onset of his renal failure seems to have been very recent and he was not receiving dialysis treatment before this admission.

Familial hypocalciuric hypercalcemia is a rare autosomal dominant disorder in which the calcium-sensing receptor of the parathyroid glands is functionally impaired such that a serum calcium level that is higher than normal is necessary to inhibit PTH synthesis and release. The calcium-sensing receptor also plays an important role in the regulation of calcium homeostasis, causing an increase in renal tubular calcium resorption that results in elevated serum calcium levels and decreased urinary calcium levels (hypocalciuria). However, familial hypocalciuric hypercalcemia is usually a clinically insignificant condition, and serum calcium levels are not as high in affected patients as they reportedly were in this patient.

Finally, lithium can increase the threshold at which calcium suppresses PTH production, producing clinical manifestations similar to those associated with hyperparathyroidism. This patient did not have a history of taking this medication, and therefore, this is an unlikely diagnosis in this case.

The first step in diagnosing PTH-dependent hypercalcemia is to measure the PTH level. This patient's PTH level was in the low-normal range, which is unlikely to cause hypercalcemia. However, it is somewhat unusual that the PTH level was not fully suppressed in a patient with a markedly elevated serum calcium level; this finding possibly suggests that he has some degree of autonomous parathyroid function (parathyroid autonomy) unrelated to his acute presentation.

PTH-INDEPENDENT HYPERCALCEMIA

There are several causes of PTH-independent hypercalcemia. Certain causes — such as the administration of total parenteral nutrition, prolonged immobilization, the milk alkali syndrome, and the administration of other specific medications (e.g., thiazides, calcium, and vitamin D and vitamin A supplements) — can be ruled out on the basis of this patient's history and laboratory test results. However, several categories of diseases that can cause PTH-independent hypercalcemia warrant further consideration, including other endocrine disorders, granulomatous diseases, and cancer.

Endocrine Disorders

The patient's thyrotropin level was slightly low, raising the possibility of hyperthyroidism; if hyperthyroidism is severe, it can lead to hypercalcemia through a thyroid-hormone–mediated increase in bone resorption. A low thyrotropin level might alternatively be explained by the euthyroid sick syndrome, and thus it would be helpful to measure the serum free thyroxine and total triiodothyronine levels to distinguish between these possibilities. Overall, the laboratory test results are inconsistent with hyperthyroidism and certainly with hyperthyroidism severe enough to cause hypercalcemia. Adrenal insufficiency is an uncommon cause of hypercalcemia and typically occurs in patients with adrenal crisis; this scenario is not consistent with this patient's presentation.

Granulomatous Diseases

Granulomatous diseases, such as sarcoidosis and tuberculosis, can also cause PTH-independent hypercalcemia.[3,4] In these conditions, the extrarenal production of 1,25-dihydroxyvitamin D by macrophages can lead to increased bone resorption and intestinal calcium absorption.[5] This patient had a normal 25-hydroxyvitamin D level, but measurement of the serum 1,25-dihydroxyvitamin D level might have been clinically useful, since it may be elevated in patients with hypercalcemia related to granulomatous diseases.[6]

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Cancer

The mechanisms that produce increased serum calcium levels in patients with cancer are generally characterized as humoral or lytic.[7,8] The aberrant production of PTH-related protein may increase bone resorption and distal renal tubular calcium resorption. Hypercalcemia that is induced by PTH-related protein occurs in patients with a variety of tumors, including squamous-cell carcinoma, adenocarcinoma of the breast or ovary, and renal-cell carcinoma. The serum level of PTH-related protein can be measured, but test results are usually not rapidly available. Some cancers, most notably lymphoma, produce 1,25-dihydroxyvitamin D in a PTH-independent manner, a process similar to that observed in granulomatous diseases. In contrast, other cancers cause hypercalcemia through an osteolytic mechanism; this occurs with some tumors that metastasize to bone (e.g., breast cancer), as well as with multiple myeloma.

RENAL FAILURE

In addition to considering possible disorders that cause hypercalcemia, we also need to explain why renal failure developed in this patient. Did this patient's renal failure represent prerenal, intrinsic renal, or postrenal disease? There was no history of recent volume depletion or hypotension to suggest a prerenal cause of kidney injury; however, chest imaging studies that were obtained during an earlier hospitalization revealed findings consistent with heart failure, which may be associated with decreased renal parenchymal perfusion that occurs as a consequence of low effective circulating volume. The patient's fractional excretion of sodium was 4.8%; in general, a value above 1% points away from prerenal causes of kidney disease.[9] The patient had benign prostatic hypertrophy and a slightly high prostate-specific antigen level, raising the possibility of postrenal obstruction due to prostate disease; however, pelvic imaging studies did not show obstruction in the urinary tract. His renal failure most likely reflected intrinsic renal disease, even though urinalysis did not reveal active sediment or muddy brown casts that would have been indicative of acute tubular necrosis.

HYPERCALCEMIA AND RENAL FAILURE

Which diseases cause both hypercalcemia and renal failure? Hypercalcemia alone can lead to renal failure through renal vasoconstriction, hypovolemia, nephrocalcinosis, and interstitial renal disease. However, histopathological examination of this patient's renal-biopsy specimen did not reveal nephrocalcinosis.

Cancer can cause both hypercalcemia and glomerular, tubulointerstitial, or vascular disease in the kidney. Multiple myeloma with light-chain deposition can certainly lead to kidney failure. Lymphoma can infiltrate the kidneys and cause impaired renal function, but there was no evidence of kidney enlargement on this patient's imaging studies. Solid tumors can cause membranous nephropathy or other paraneoplastic glomerulopathies.

Granulomatous diseases can also cause both hypercalcemia and renal failure. Although clinical manifestations of renal sarcoidosis are observed in only 1 to 2% of affected patients, up to 50% of autopsies of patients with sarcoidosis reveal granulomas or mononuclear-cell infiltrates in the kidneys. This patient had a history of a positive tuberculin skin test, and *Mycobacterium tuberculosis* infection can lead not only to renal granulomas but also to glomerular disease, interstitial nephritis, and secondary amyloidosis. However, because the patient did not have the classic symptoms of tuberculosis (i.e., fever, cough, and night sweats) and was neither immunosuppressed nor chronically debilitated, reactivation or miliary tuberculosis is relatively unlikely.

The patient's demographic characteristics make cancer epidemiologically more likely than granulomatous disease; sarcoidosis is most likely to occur in persons who are younger than 40 years of age and female. The patient had a history of smoking, which conferred an increased risk of lung cancer and other cancers. He had lucent bone lesions in the skull and legs, as well as a monoclonal gammopathy, which occurs in approximately 5% of persons older than 70 years of age. However, I believe these findings are of uncertain clinical significance, because examination of the bone marrow–biopsy specimen showed only 7% plasma cells, whereas specimens from patients with multiple myeloma typically show 10% or more plasma cells.[10,11] Furthermore, if the hypercalcemia were due to multiple myeloma, I suspect that an even larger percentage of plasma cells would have been present in the bone marrow–biopsy specimen. The patient had a high angiotensin-converting–enzyme level, which is

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seen in up to 75% of patients with sarcoidosis, although false positive results can occur, even in patients with tuberculosis or uremia. He also had increased levels of serum alkaline phosphatase and γ-glutamyl transpeptidase, findings suggestive of liver disease, which could be either a metastatic cancer or a granulomatous infiltration similar to that observed in the kidney. Hilar and mediastinal adenopathy also could be manifestations of either cancer or granulomatous disease, but if the adenopathy were due to cancer, I would have expected it to progress over a 2-year period rather than to appear stable on longitudinal chest imaging. Furthermore, histopathological examination of the renal-biopsy specimen showed interstitial nephritis and mononuclear-cell and granulomatous inflammation; these findings lead us toward a diagnosis of granulomatous disease.

Taken together, the clinical features observed in this patient fit best with a diagnosis of sarcoidosis, even though the demographic characteristics would be atypical for this diagnosis. I suspect that the procedure performed to confirm this diagnosis was a lymph node biopsy.

Dr. Eric S. Rosenberg (Pathology): Dr. Kalim, what was your clinical impression when you initially evaluated this patient?

Dr. Kalim: Early in this patient's clinical course, we were concerned about the possibility of IgM myeloma; however, hypercalcemia and lytic lesions are not typical in patients with IgM myeloma, the monoclonal spike was quite low, and the amount of plasma cells in the bone marrow was less than 10%. The clonal plasma-cell process was therefore characterized as a monoclonal gammopathy of undetermined significance, which was not thought to explain his clinical presentation. Therefore, our top diagnostic consideration was granulomatous disease due to either tuberculosis or sarcoidosis, and we arranged for the patient to undergo a lymph node biopsy.

CLINICAL DIAGNOSIS

Granulomatous disease due to either tuberculosis or sarcoidosis.

DR. NEIL R. POWE'S DIAGNOSIS

Granulomatous disease, most likely due to sarcoidosis.

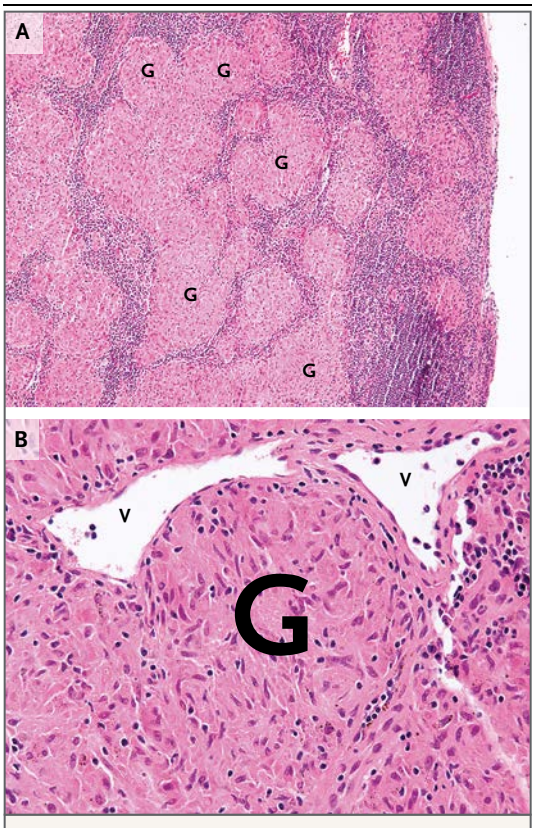

Figure 3. Lymph Node–Biopsy Specimen (Hematoxylin and Eosin).

Pathological examination of a paratracheal lymph node was performed. Panel A shows replacement of most of the lymph node by confluent, compact, non-necrotizing granulomas (G); a small rim of nodal cortex is present along the right edge. Panel B shows a discrete granuloma (G) impinging on a vessel (V) in the lymph node.

PATHOLOGICAL DISCUSSION

Dr. Mark: The diagnostic procedure was a biopsy of a paratracheal lymph node. On histopathological examination, the node was subtotally replaced by compact, confluent, non-necrotizing granulomas with microfocal necrosis (Fig. 3A). A discrete granuloma impinged on a lymphatic vessel in the node (Fig. 3B). These findings were consistent with sarcoidosis. The degree of necrosis was within the range that is commonly encountered in sarcoidosis, and stains and cultures for organisms were negative. Lymph node biopsy, whether of an enlarged peripheral lymph node[12] or an enlarged mediastinal lymph node,[13] remains a standard procedure for the definitive diagnosis of sarcoidosis.

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FOLLOW-UP

Dr. Kalim: Because the stains for acid-fast bacilli that were performed on bronchial washings, urine specimens, and the lymph node–biopsy specimen were all negative, the patient's positive tuberculin skin test was interpreted as evidence of latent (rather than active) tuberculosis infection. Initially, both isoniazid and rifampin were administered, but when all mycobacterial cultures remained negative after 2 months, rifampin was discontinued. The patient received a total of 9 months of isoniazid therapy for the treatment of latent tuberculosis infection.

After the results of the lymph node biopsy were known, oral glucocorticoid therapy was initiated for the treatment of sarcoidosis. The patient received low-dose glucocorticoids for 2.5 years, and his renal function improved and stabilized; his baseline creatinine level is now 1.6 mg per deciliter (141 μmol per liter), which is consistent with stage 3 chronic kidney disease. Approximately 2 years ago, the glucocorticoids were discontinued. Hypercalcemia has not recurred, the results of serum protein electrophoresis are unchanged, and the patient has not required any additional therapies.

It is interesting to note that the cognitive decline and choreiform movements that were being evaluated at the time of the current admission improved when the patient was treated with glucocorticoid therapy, raising questions about the possibility of neurosarcoidosis. At present, the patient is thought to have early Alzheimer's disease, and the choreiform movements have not recurred.

FINAL DIAGNOSIS

Sarcoidosis.

The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Department of the Army, the Department of Defense, or the U.S. Government.

This case was presented at the Harvard Medical School postgraduate course "Internal Medicine: Comprehensive Review and Update 2013," directed by Ravi I. Thadhani, M.D., M.P.H., and Sekar Kathiresan, M.D.

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

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