Renal Failure Found during the Follow-up of Sarcoidosis: The Relevance of a Delay in the Diagnosis of Concurrent Hypercalcemia

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Abstract

We herein present a case of relapsed sarcoidosis with a deteriorated renal function accompanied by hypercalcemia, nephrolithiasis, and a ureteral stone in a woman with a history of ocular sarcoidosis. The ocular involvement appeared to be well controlled for a long period of time with a topical ophthalmic steroid; however, we believe that the absence of apparent recrudescence could have led to the delay in our diagnosis of relapse of the disease during the follow-up period. The conundrums regarding longitudinal surveillance for both evaluating the disease activity and determining the necessity of therapeutics are also discussed.

Key words: hypercalcemia, hypercalciuria, ocular sarcoidosis, hydronephrosis, chronic kidney disease


Introduction

The clinical presentation, natural history, and prognosis of sarcoidosis are quite variable and show a propensity to wax and wane, either spontaneously or in response to immunomodulation (1). Most patients present with the traditional combination of bilateral hilar lymphadenopathy, pulmonary parenchymal disease, and cutaneous or ocular lesions, while virtually any organ system may be involved (2). Occasionally, renal abnormalities may be determined to be the initial manifestation or to have occurred in the course of previously diagnosed sarcoidosis (3). We herein describe the case of a patient in which the deterioration of renal function was accompanied by hypercalcemia, hypercalciuria, nephrolithiasis, and a ureteral stone in a woman with a history of ocular sarcoidosis without pulmonary parenchymal disease. The delay in the diagnosis of relapse of the disease during the follow-up period played a role in the establishment of the patient’s clinical manifestations.

Case Report

A 67-year-old woman with a history of sarcoid uveitis accompanied by bilateral hilar lymphadenopathy and with no evidence of pulmonary parenchymal disease was referred and admitted to our hospital at the end of July 2013 due to the progressive deterioration of her renal function, which was associated with hypercalcemia. She had been diagnosed with sarcoid uveitis nine years previously. At the time, there were no signs of renal failure and her serum creatinine (sCr) level was 0.6 mg/dL. Her disease was treated at another hospital with oral prednisolone (PSL), which was administered for four months, and the administration of an ophthalmic corticosteroid. The treatment successfully controlled the disease activity; however, her chest radiography findings did not change during the observation period. No abnormalities were recognized in the patient’s serum calcium (Ca) levels until July 2011. The data from the two years that followed were unavailable. In the beginning of December 2012, the patient remained asymptomatic with the continued use of
On admission, the patient was alert and oriented. Her blood pressure was 120/77 mmHg, her pulse was regular at 65 beats/min, and her temperature was 36.6°C. A laboratory examination revealed the following results: hemoglobin, 10.5 g/dL; hematocrit, 30.5%; platelet count, 23.1×10^9/μL; blood urea nitrogen, 34 mg/dL; sCr, 2.70 mg/dL; uric acid, 8.3 mg/dL; total protein, 7.5 g/dL; serum albumin, 3.6 g/dL; sodium, 142 mmol/L; potassium, 4.5 mmol/L; chloride, 109 mmol/L; Ca 12.5 mg/dL; Ca corrected by the formula of Payne et al. (calcium (cCa)) (4), 12.9 mg/dL; phosphorus, 3.8 mg/dL; alkaline phosphatase, 163 mU/mL; immunoglobulin (Ig) G, 2,217 mg/dL; IgA, 287 mg/dL; and IgM, 22 mg/dL. The serum levels of intact parathyroid hormone (PTH), PTH-related protein, 1,25-dehydroxyvitamin D3 [1,25(OH)₂-vitamin D³], angiotensin-converting enzyme (ACE), lysozyme, and bone tartrate-resistant acid phosphatase-5b (TRACP-5b) were 10 pg/mL (reference range: 10-65 pg/mL), 2.0 pmol/L (reference range: <1.1 pg/mL), 64.8 pg/mL (reference range: 20-60 pg/mL), 22.6 mU/mL (reference range: 8.3-21.4 mU/mL), 29.9 μg/mL (reference range: 5-10.2 μg/mL), and 531 mU/dL (reference range: 120-420 mU/dL), respectively. A 24-hour urine specimen was found to contain 0.17 g and 330 mg of protein and Ca, respectively. The fraction of excretions of sodium (FEson) and urea (FEurea) were 6.92% and 64.9%, respectively, while that of Ca (FECa) was 0.27%. The urinary excretion of β2-microglobulin (β2MG) and N-acetyl-beta-D-glucosaminidase (NAG) were 31,389 μg/L (reference range: <200 μg/L) and 28.2 U/g-Cr (reference range: 0.9-2.4 U/g-Cr), respectively. The amount of urinary type I collagen cross-linked N-telopeptide (NTx) was 131.9 nmol BCE/mmol/Cr (reference range: 9.3-54.3 nmol BCE/mmol/Cr). A skin tuberculin test was negative. Chest radiography showed bilateral hilar lymphadenopathy. Bilateral nephrocalcinosis, pelviureteral dilatation, and a left ureteral stone were noted and mediastinal lymph nodes were found to be enlarged in a subsequent computed tomography (CT) scan (Fig. 1A-C). Although a radionuclide gallium (Ga) scintigram did not detect the abnormal accumulation of radiotracer in the kidneys, an accumulation was detected in a dependent area of the thoracic lymphadenopathies (Fig. 1D). Ophthalmological screening revealed bilateral peripheral anterior synechia; there was no evidence of active ocular sarcoidosis.

A double J stent was immediately placed in the left ureter and aggressive saline hydration, furosemide diuresis and subcutaneous calcitonin were started as an empirical treatment for hypercalcemia. The patient’s sCr level transiently increased to approximately 3.6 mg/dL and gradually decreased thereafter. The patient failed to respond to the treatment for hypercalcemia. A renal biopsy was performed on hospital day 15. The biopsy, which consisted of three cores of renal parenchyma with eighteen glomeruli, exhibited atrophic changes in the structure of the tubules and interstitial fibrosis, as well as lymphocytic tubulointerstitial nephritis without granulomas with several intratubular Ca deposits that were consistent with nephrocalcinosis (Fig. 2). With the exception of two glomeruli, which were globally sclerotic, no glomerular changes were noted. Electron and immunofluorescence microscopy revealed no evidence of immune complex deposits. According to these clinical and laboratory findings, the patient was diagnosed with a relapse of sarcoidosis complicated by hypercalcemia. Treatment with oral PSL (40 mg/day) was started from hospital day 36, which resulted in further decreases in the serum levels of Ca, ACE, and 1,25(OH)₂-vitamin D³, despite the lack of sufficient improvement in her renal function (Fig. 3). No abnormalities in the patient’s serum thyroid-stimulating hormone (TSH) level (0.8 μU/mL, reference range: 0.45-3.33 μU/mL) or free T4 level (1.1 ng/dL, reference range: 0.84-1.44 ng/dL) were found, despite a decreased free T3 level of 1.18 pg/mL (reference range: 2.11-3.51 pg/mL) on hospital day 48. Overall, her clinical course was favorable, with the exception of the development of voiding difficulty, which became overt in the middle of September 2013 and was successfully managed with oral distigmine bromide and pra-
Discussion

The recurrence of sarcoidosis after the long-lasting complete resolution of the clinical, radiological, and other markers of activity is considered to be a rare event (5); although it has been recognized that a reduction in the dose or termination of systemic corticosteroid therapy is often followed by recrudescence or the relapse of the disease (6, 7). Most relapses occur between two and six months after termination of the systemic steroid therapy; however, late relapses are not exceptional and occur at more than 12 months after the discontinuation of treatment in 20% of patients with induced remission (6). The ocular involvement of our patient appeared to be well controlled for a long period of time with a topical ophthalmic steroid, despite the fact that she had concurrently received oral steroids for four months. However, it has been proposed that the long-term use of corticosteroid eye drops may delay the spontaneous remission of pulmonary sarcoidosis (8). Although it is not clear whether the topical ophthalmic steroid had an impact on the pulmonary and/or thoracic sarcoid lesions of the current patient, its...
Clinical benefit in the overall management of sarcoidosis may require careful evaluation.

Sarcoidosis may be associated with a broad spectrum of renal manifestations (3, 9, 10). Interstitial granulomatous nephritis as well as various kinds of glomerulopathies may be implicated (3, 9, 10); however, renal histological examinations may fail to demonstrate the scattered granulomatous tissue due to sampling effects (3, 11). On the other hand, an aberrant Ca metabolism with hypercalcemia and/or hypercalciuria, which can be linked to elevated bone resorption as well as increased intestinal absorption of Ca mediated by the accelerated granulomatous 1,25(OH)2-vitamin D3 production (12, 13), has been identified as the most important cause of renal abnormalities in patients with sarcoidosis (3, 9). Thus, the increased levels of urinary NTx and serum TRACP-5b at the time of admission might have mirrored the concurrently accelerated bone turnover (14). Hypercalcemia may be linked to a decline in the glomerular filtration rate, urinary sodium wasting with polyuria and volume depletion, acute tubular necrosis induced by intracellular calcium overload, and tubular obstruction by calcium precipitates, while hypercalciuria predisposes patients with sarcoidosis to nephrolithiasis and obstructive uropathy (3, 5, 6, 15). In this case, we failed to confirm the presence of granulomatous tissue in the renal biopsy specimen. It is therefore difficult to evaluate the precise pathogenesis of the patient’s renal parenchymal injuries. Nevertheless, the renal pathological view and the clinical course, as well as the laboratory and radiological findings, encouraged us to conclude that the calcemic nephropathy and concurrent obstructive uropathy would be major adverse modulators of the renal function. Bilateral hydroureteronephrosis despite the unilateral nature of the ureterolith at the initial presentation might be linked to latent urinary retention. The etiological background of bilateral hydroureteronephrosis in the current patient remains to be elucidated; however, a post-stroke mechanism is a potential candidate (16), since she had a medical history of ischemic stroke, which was revealed approximately two years before her admission. Meanwhile, the radiological findings and her clinical picture during the observation period did not appear to support the concurrence of ureteral sarcoidosis, which can be associated with a ureteral obstruction leading to the development of hydroureteronephrosis (17). Finally, we confirmed that bilateral hydroureteronephrosis of the current patient persisted, even after the recovery of the renal function, using serial CT (data not shown), implying the marginal role of such structural disorders in renal function abnormalities.

Although recrudescence of the ocular involvement was absent, the diagnosis of the relapse of sarcoidosis as the cause of our patient’s hypercalcemia associated with renal failure was straightforward after confirming the presence of the abnormal thoracic uptake of radionuclide Ga, the elevated serum level of ACE and hypercalciuria (18). The discordance in the manifestations at the initial onset and at relapse (which occurred in the present case), may not be exceptional. Such differences have been shown in 7.35% of patients with relapsed sarcoidosis (6, 7). Consequently, one may argue that the clinical picture of the current patient, including the disturbance of Ca homeostasis, renal failure, nephrolithiasis, urolithiasis, and the relapse of sarcoidosis, are neither surprising nor worth being described in the literature (3, 9, 10, 19). However, we are of the opinion that the reports on the pattern of relapse and the late course of the disease remain insufficient and the clinical significance of our experience must be evaluated more carefully. Indeed, there are few reports in the literature which describe the relapse of sarcoidosis, with the above-described manifestations, after a long period of quiescence in patients with sarcoid uveitis (3, 5, 7, 20).

Considering the differential diagnosis of hypercalcemia (21), our initial workup might not be sufficient in terms of screening for the thyroid and/or adrenal function. The results of the thyroid function test might thus be modulated by the PSL treatment through the restriction of free T3 production from T4, thereby resulting in reduced serum levels of free T3 (22), while the presence of hyperthyroidism would not be supported. Moreover, we failed to confirm the features of adrenal insufficiency, such as hypotension, pigmentation, hypoglycemia, eosinophilia, and/or lymphocytosis (data not shown) (23). These facts led us to conclude that the role of thyroid- and/or adrenal-dependent pathology may be trivial. Alternatively, or in addition, one may argue that our initial management for hypercalcemia might not be an appropriate strategy since the routine administration of a loop diuretic may no longer be recommended as an emergency management for hypercalcemia (24). However, there was a concern that the impaired renal function of the present patient could have led to volume overload due to aggressive saline hydration. Moreover, the data regarding FE\textsubscript{Na} and FE\textsubscript{cr}, as well as the ratio of BUN to serum Cr of 12.6 on admission, led us to regard our patient as having an euvoletic status (25, 26). Consequently, we believe that the timely initiation of aggressive treatment combined with furosemide for symptomatic hypercalcemia accompanied by a loss of appetite would be justified in the current case, although the clinical course might not allow us to precisely evaluate the benefits of such a therapeutic regimen.

Our case may also illustrate the conundrum regarding longitudinal surveillance both for evaluating the disease activity and determining the need for therapeutics. In the current case, the careful review of the patient’s clinical record led us to confirm that the serum Ca levels in 2009 and 2011 were 9.9 mg/dL and 9.7 mg/dL, respectively. Unfortunately, the patient’s records lacked longitudinal data regarding her serum and/or urinary levels in the two years before she was admitted to our hospital, thereby precluding us from evaluating the precise time course of concurrent hypercalcemia and/or hypercalciuria. However, we feel it is reasonable to consider that the presence of abnormal calcification within the nephroureteral territory was linked to prolonged hypercalcemia and/or hypercalciuria resulting from the relapse of
sarcoidosis (9, 15), and the diagnostic and therapeutic delay of such pathologies could have resulted in the irreversible deterioration of the renal function of the current patient. Indeed, the recovery of the renal function after the initiation of oral corticosteroid treatment, which has been regarded as the therapy of choice for sarcoidosis (1, 16, 27), appeared to be insufficient, despite the prompt improvement of the patient’s serum levels of Ca. Therefore, the appropriate management may vary considerably with the etiology and severity of hypercalcemia; however, the simultaneous administration of bisphosphonate and/or denosumab, which has been identified as a noble therapeutic option for some subsets of patients with the disease (13, 21, 28), might have a beneficial effect in terms of the link between the administration of pharmacological-dose corticosteroids and the acceleration of bone resorption (29). In the current patient, the confirmation of dental decay, which resulted in tooth extraction during the observation period, precluded us from using these agents as adjunct management due to the risk that the patient might concurrently develop osteonecrosis of the jaw, although such a policy may be controversial (30-32). Thus, a more extensive evaluation regarding the clinical benefit of these agents combined with systemic corticosteroids among patients with sarcoidosis complicated by hypercalcemia is necessary.

Finally, the major concern in making decisions regarding the treatment of sarcoidosis should be to determine the extent and activity of the disease, which can predispose various organs to permanent damage (1, 20). Currently, a urinalysis and the measurement of serum Ca levels, which can be a surrogate for the disease activity, and several renal parameters, including BUN and serum Cr, are recommended in the initial workup of patients with sarcoidosis (1). In addition, no one would argue against the importance of the periodic evaluation of such parameters in some subsets of patients with sarcoidosis (1, 14). Nevertheless, such timely screenings may not necessarily be thoroughly performed in ordinary clinical settings - as was the case in the current patient. We believe that the accumulation of more experience with sarcoidosis patients with various manifestations of calcification, as well as serum and/or urinary Ca abnormalities, will help to determine the optimal intervals for longitudinal surveillance and flexible follow-up policies for the disease and establish appropriate therapeutic strategies.

The authors state that they have no Conflict of Interest (COI).

References


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