

## Case Report

# Progressive renal insufficiency, hypercalcaemia, bicytopenia and a history of breast cancer

Sebastian Letterer<sup>1</sup>, Ulrich Lindner<sup>1</sup>, Heinz-Wolfram Bernd<sup>2</sup>, Florian M. Vogt<sup>3</sup>, Udo Helmchen<sup>4</sup>, Hendrik Lehnert<sup>1</sup> and Christian S. Haas<sup>1</sup>

<sup>1</sup>Department of Medicine I and Nuclear Medicine, University of Luebeck, Luebeck, Germany, <sup>2</sup>Department of Pathology and Nuclear Medicine, University of Luebeck, Luebeck, Germany, <sup>3</sup>Clinic for Radiology and Nuclear Medicine, University of Luebeck, Luebeck, Germany and <sup>4</sup>Kidney Registry, Institute of Pathology, University Hospital Hamburg-Eppendorf, Germany

Correspondence and offprint requests to: Christian S. Haas; E-mail: cs\_haas@yahoo.com

## Abstract

Sarcoidosis can affect all organs and may mimic a variety of other diseases. In the absence of typical pulmonary features, extrapulmonary manifestations may be difficult to diagnose. We describe here the very uncommon case of a patient with mild pulmonary involvement but distinct renal, bone marrow and lymph node sarcoidosis. Treatment with glucocorticoids significantly improved kidney function and normalized serum calcium levels as well as the blood count. This case underscores the importance of sarcoidosis to be considered as a differential diagnosis of renal failure associated with hypercalcaemia and nephrocalcinosis. Bone marrow involvement should always be suspected if mono-, bi- or pancytopenia coexist.

**Keywords:** bone marrow; interstitial nephritis; renal insufficiency; sarcoidosis

## Background

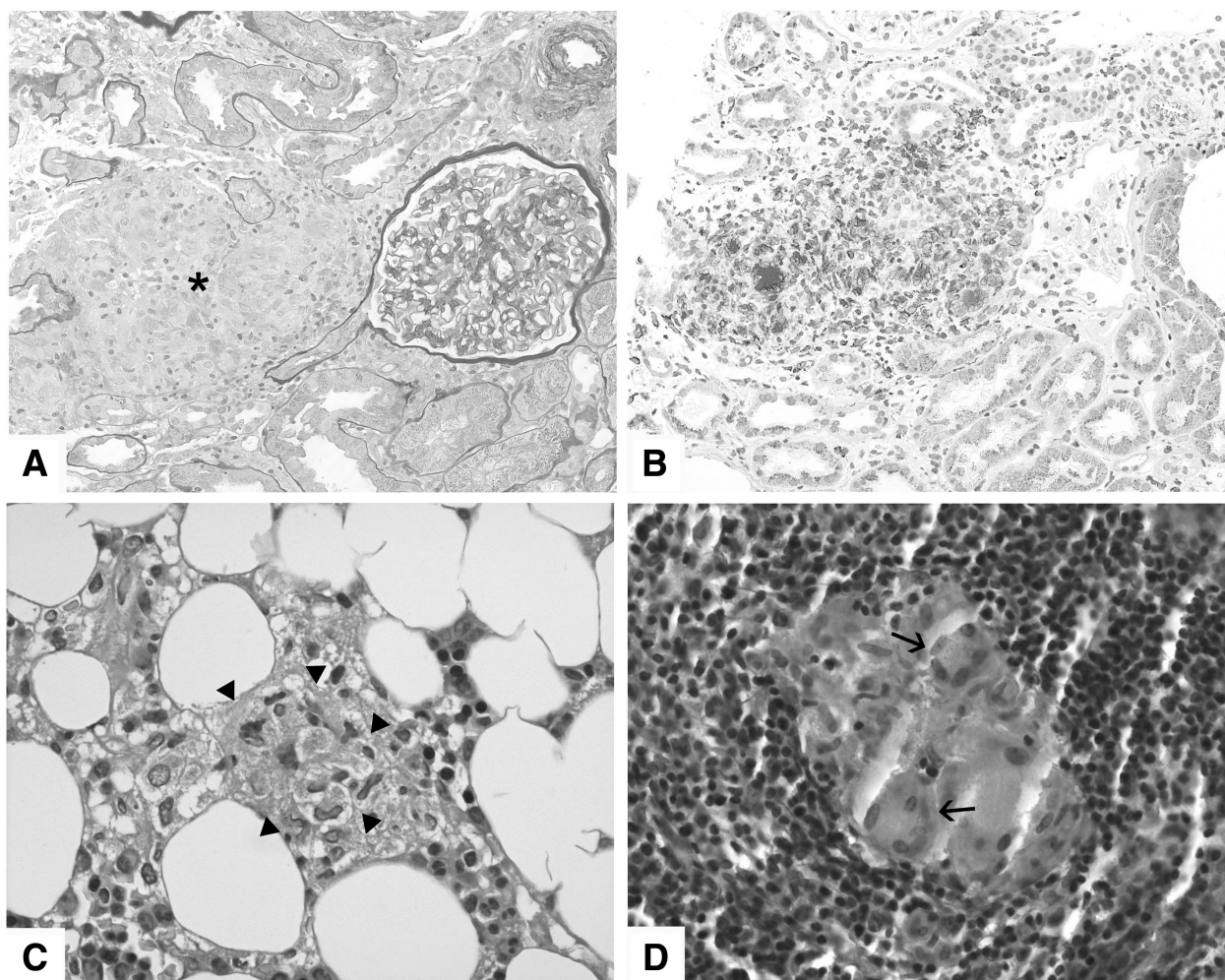
Progressive renal failure is a common scenario in clinical practice. In many cases, the cause is obvious. In some cases, however, the patient's history and clinical presentation may be misleading. We report here the case of a woman admitted for progressive renal failure with a history of hypertension, osteoporosis and recent therapy for breast cancer, presenting with significant hypercalcaemia, hyperphosphataemia and bicytopenia. Further evaluation revealed an unexpected diagnosis.

## Case report

A 70-year-old woman with a history of hypertension and osteoporosis presented with progressive renal insufficiency, abnormal fatigue for several months and increasing shortness of breath during exercise. Five months previously, an invasive ductal breast carcinoma (pT2, pTis, pN0, cM0

and R0) had been diagnosed, and the patient underwent breast-conserving tumour resection, followed by adjuvant radiotherapy and treatment with a non-steroidal aromatase inhibitor. On admission, the patient appeared to be in a good general condition (weight 53 kg, height 168 cm and BMI 19 kg/m<sup>2</sup>) and seemed only slightly affected. Vital signs were normal (blood pressure 130/60 mmHg and heart rate 80 bpm), and physical examination was unremarkable. The patient's medication included letrozole, calcium and vitamin D<sub>3</sub>. Previous administration of alendronate had been stopped before admission. Laboratory testing showed impaired renal function with a creatinine of 297 µmol/L and an estimated glomerular filtration rate (GFR) of 14 mL/min/1.73 m<sup>2</sup>. Serum calcium level was significantly elevated (3.6 mmol/L) in the presence of slightly lowered serum albumin (31 g/dL). A blood count showed normocytic anaemia (haemoglobin 11.5 g/dL), leucocytopenia (2840/µL) and a normal platelet count; a differential blood count revealed significant lymphocytopenia (227/µL). Further biochemical tests demonstrated hyperphosphataemia (2.4 mmol/L) but normal values for parathyroid hormone and C-reactive protein. Urinalysis showed signs of prevailing tubulointerstitial nephritis with minor leucocyturia, predominant tubular proteinuria and mild haematuria.

A diagnostic work-up was performed to establish the cause of hypercalcaemia and bicytopenia and to identify the underlying renal disease. A skeletal scintigraphy ruled out bone metastatic disease, and abdominal ultrasound did not show any isolated metastases or a tumour mass. Renal ultrasound demonstrated kidneys of normal size with hyper-echoic parenchyma and hypoechoic pyramids as well as signs of nephrocalcinosis. Computed tomography of the chest revealed two new very small nodular lesions in both upper lobes; however, there was no notion of enlarged intrathoracic lymph nodes. Spirometric testing was within the normal range (FEV1 85%, VCin 99%, FEV1/VCin 90% and pO<sub>2</sub> 84 mHg). Subsequent bronchoscopy showed a macroscopically normal bronchial system, and bronchoalveolar lavage did not reveal suspicious cells or any infec-



**Fig. 1.** (A, B) Renal histology: A. Epithelioid cell granuloma (asterisk) with multinucleated giant cells, adjacent to a glomerulus (PAS staining); B. CD68 staining depicting macrophages, epithelioid cells and multinucleated giant cells (APAAP method); von Kossa staining demonstrated microcalcifications within the tubulointerstitium (not shown). (C) Bone marrow histology, depicting moderate plasmacytosis and a non-caseating granuloma (arrowheads). Ziehl–Neelsen staining was negative (not shown). (D) Lymph node histology obtained 5 months previously for breast cancer staging, demonstrating tumour-free sentinel lymph nodes and an epithelioid cell granuloma with giant cells (arrows).

tious pathogen but a lymphocytic cell profile with an elevated T4/T8 ratio of 5.5. A renal biopsy was performed: histopathology displayed a few moderate epithelioid cell granulomas with interstitial nephritis, slight nephrocalcinosis and moderate focal tubular atrophy, suggesting sarcoid nephropathy (Figure 1A and B). Bone marrow biopsy demonstrated impaired haematopoiesis with slight siderosis, moderate plasmacytosis and surprisingly also an epithelioid cell granuloma (Figure 1C), consistent—although non-specific—with manifestation of sarcoidosis. Immunophenotyping of the bone marrow revealed CD138/CD19-positive plasma cells, but no light chains or any other B- or T-cell clonal disease. Revision of a lymph node biopsy, previously performed for staging of the breast cancer, also revealed an epithelioid cell granuloma (Figure 1D). Further laboratory testing was negative for immunological antibodies, including antinuclear antibodies and c- and p-ANCA, but showed elevated serum levels for angiotensin-converting enzyme (137 U/L, normal <52). Echocardiography demonstrated moderate left ven-

tricular hypertrophy with normal systolic function and slight diastolic dysfunction.

Altogether, a diagnosis of sarcoidosis with renal, pulmonary, bone marrow and lymph node involvement was made, while cardiac manifestation was suspected. Treatment with prednisolone resulted in significantly improved renal function within several days, normalized calcium and phosphate values, and led to a haemoglobin and leucocyte count within the normal range. Follow-up studies 3 months later showed an almost normal serum creatinine level of 108  $\mu\text{mol/L}$  with an estimated GFR of 46 mL/min/1.73 m<sup>2</sup>, a normalized ACE level and regressive pulmonary lesions.

## Discussion

Nephrocalcinosis is usually an incidental finding in ultrasound or CT imaging or in a renal biopsy specimen, and may both cause and sustain progressive renal insufficiency. Any disorder leading to high calcium levels and/or hyper-

calciuria may result in renal calcium deposition, thereby promoting nephrolithiasis or renal parenchymal damage with subsequent reduced renal function. Thus, nephrocalcinosis demands further evaluation with identification of the underlying cause to provide a therapeutic approach [1].

In our patient, the combination of hypercalcaemia and a previous diagnosis of breast cancer initially suggested bone metastasis. However, an unremarkable skeletal scintigraphy did not support this idea. Primary hyperparathyroidism was ruled out by normal parathyroid hormone levels. Although calcium and vitamin D supplementation in association with renal insufficiency were consistent with vitamin D intoxication or milk-alkali syndrome as a possible cause for hypercalcaemia, stopping the medication did not normalize calcium homeostasis. Finally, other differential diagnoses had to be taken into account: since history, clinical presentation and biochemical findings were not compatible with Addison's disease, inflammatory bowel disease or thyrotoxicosis, sarcoidosis was considered the most likely cause.

Clinical manifestation and outcome of sarcoidosis are highly variable, and the diagnosis is often delayed [2]. The typical primary manifestation is the lung, often associated with involvement of skin, eyes, and the reticuloendothelial or musculoskeletal system. Infrequently, the heart, kidney and liver as well as endocrine and exocrine glands are affected [3]. Bone marrow involvement is very rare but may be underdiagnosed [4,5].

In our patient, the combination of hypercalcaemia, nephrocalcinosis and urinalysis was suspicious for sarcoid nephropathy, and renal biopsy established the diagnosis. Histopathological evidence of non-purulent destructive tubulointerstitial nephritis supported the diagnosis, with granulomatous infiltration being confirmative [6,7]. Renal disease in sarcoidosis always requires intervention since lack of treatment may allow progression to chronic renal failure. In the present case, renal histology demonstrated not only calcinosis but also reversible tubular damage: administering corticosteroids reduced serum calcium levels and hypercalciuria, thereby preventing further renal damage and significantly improved kidney function. Unfortunately, renal involvement is usually steroid-dependent with a decline in kidney function when therapy is stopped [8]. In the present case, this may only be determined with a longer follow-up.

Pulmonary infiltration and nodular lesions together with a high T4/T8 ratio in bronchoalveolar lavage and the absence of infection also pointed to sarcoidosis despite the lack of intrathoracic lymphadenopathy. However, the extent of pulmonary sarcoidosis would not have justified the corticosteroid treatment, and in the context of previously diagnosed breast cancer, metastatic disease could not be definitively ruled out. Since sarcoidosis may even mimic metastatic malignancy, histological evidence may be important [9]. Eventually, a short-term follow-up with CT imaging was helpful to distinguish between both disease entities.

Surprisingly, bicytopenia was shown to be the result of bone marrow sarcoidosis. With respect to previous breast cancer, bone marrow cancer infiltration may have been the most likely diagnosis; other differential diagnoses included myelodysplastic syndrome and renal anaemia.

Surprisingly, bone marrow histology and phenotyping demonstrated an epithelioid cell granuloma and plasmocytosis consistent with sarcoidosis. Conceivably, bone marrow involvement is frequently underdiagnosed since diagnostic biopsy sites are most often intrapulmonary, based on the common clinical presentation [5,10].

Of interest, retrospective analysis of the lymph node biopsies obtained a few months previously also revealed a non-caseating epithelioid cell granuloma. While epithelioid granulomas occasionally are a manifestation of a lymphoma [11], the so-called sarcoid-like lesions are often described in association with various malignancies, such as melanoma, breast cancer or lung cancer [12,13]. In the present case, the pathological changes probably reflected sarcoid manifestation in the reticuloendothelial system, mimicking metastatic disease [9]. However, an association of sarcoidosis with cancer has been previously reported several times [14–17].

Finally, an elevated serum ACE was supportive of the diagnosis: up to 75% of untreated patients have increased serum levels [18]. Other disorders with granulomas in the kidney were excluded: the absence of c-ANCA antibodies or typical clinical signs as well as normal C-reactive protein made vasculitis, such as Wegener's granulomatosis, an unlikely diagnosis; specific stains in histology ruled out an infectious disease.

*Conflict of interest statement.* None declared.

## References

1. Vervaeck BA, Verhulst A, D'Haese PC *et al.* Nephrocalcinosis: new insights into mechanisms and consequences. *Nephrol Dial Transplant* 2009; 24: 2030–2035
2. Judson MA, Thompson BW, Rabin DL *et al.* The diagnostic pathway to sarcoidosis. *Chest* 2003; 123: 406–412
3. Baughman RP, Teirstein AS, Judson MA *et al.* Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001; 164: 1885–1889
4. Yanardag H, Pamuk GE, Karayel T *et al.* Bone marrow involvement in sarcoidosis: an analysis of 50 bone marrow samples. *Haematologia (Budap)* 2002; 32: 419–425
5. Mahevas M, Le Page L, Salle V *et al.* Thrombocytopenia in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2006; 23: 229–235
6. Mahevas M, Lescure FX, Boffa JJ *et al.* Renal sarcoidosis: clinical, laboratory, and histologic presentation and outcome in 47 patients. *Medicine (Baltimore)* 2009; 88: 98–106
7. Monge M, Miquel O, Dugardin F *et al.* Sarcoidosis and the kidney: not only the granulomatous interstitial nephritis. *Clin Nephrol* 2009; 71: 192–195
8. Rajakariar R, Sharples EJ, Raftery MJ *et al.* Sarcoid tubulo-interstitial nephritis: long-term outcome and response to corticosteroid therapy. *Kidney Int* 2006; 70: 165–169
9. Waanders F, van Hengel P, Krikke A *et al.* Sarcoidosis mimicking metastatic disease: a case report and review of the literature. *Neth J Med* 2006; 64: 342–345
10. Teirstein AS, Judson MA, Baughman RP *et al.* The spectrum of biopsy sites for the diagnosis of sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2005; 22: 139–146
11. Lerza R, Schenone E, Barsotti BP *et al.* Epithelioid granulomas as main clinical manifestation at the outset of non-Hodgkin's lymphoma: report of two cases. *Oncol Res* 2002; 13: 55–59
12. Steinfurt DP, Irving LB. Sarcoidal reactions in regional lymph nodes of patients with non-small cell lung cancer: incidence and implications for minimally invasive staging with endobronchial ultrasound. *Lung Cancer* 2009; 66: 305–308

13. Robert C, Schoenlaub P, Avril MF *et al.* Malignant melanoma and granulomatosis. *Br J Dermatol* 1997; 137: 787–792
14. Abdel-Galiil K, Anand R, Sharma S *et al.* Incidence of sarcoidosis in head and neck cancer. *Br J Oral Maxillofac Surg* 2008; 46: 59–60
15. Chalasani P, Vohra M, Sheagren JN. An association of sarcoidosis with hepatocellular carcinoma. *Ann Oncol* 2005; 16: 1714–1715
16. Gooneratne L, Nagi W, Lim Z *et al.* Sarcoidosis and haematological malignancies: is there an association? *Br J Haematol* 2008; 141: 260–262
17. Serratrice J, Granel B, Swiader L *et al.* Sarcoidosis preceding chronic myelomonocytic leukemia. Report of two cases. *Dermatology* 2002; 205: 409–412
18. Studdy PR, Bird R. Serum angiotensin converting enzyme in sarcoidosis—its value in present clinical practice. *Ann Clin Biochem* 1989; 26: 13–18

*Received for publication: 1.8.10; Accepted in revised form: 1.10.10*