A challenging case of renal function decline in a patient with malignant mesothelioma

P. Pateinakis¹
K. Bantis¹
A. Vossos¹
A. Lysitska¹
E. Manou¹
P. Kyriklidou¹
E. Mitsopoulos¹
I. Efstratiou²
D. Papadopoulou¹

Abstract

Oncology patients often present with renal function decline, which is usually tumor or treatment related. A patient with relapsing malignant pleural mesothelioma, initially treated by surgical excision, complicated by wound dehiscence due to Staphylococcus aureus infection, was admitted to the nephrology department because of impaired renal function, microhematuria and non-nephrotic proteinuria. The previous month he had received chemotherapy with carboplatin and pemetrexed. ANCA, antiMPO, antiPR3 and anti-GBM were negative. After initial response to steroid treatment for presumed acute tubulointerstitial nephritis, he relapsed on fast steroid taper. A renal biopsy revealed pauci-immune necrotizing glomerulonephritis. There was good response to oral cyclophosphamide and steroids. After two years of follow up the renal disease remains in remission, despite repeated chemotherapy for recurrence of malignancy.

Λέξεις κλειδιά: ANCA, cancer, crescentic glomerulonephritis, mesothelioma, oncology, staphylococcus.

Introduction

Loss of renal function in oncology patients may result from prerenal, renal and post renal causes, which are usually related to malignancy, its treatment or associated complications¹. Correct identification of the cause is essential for effective treatment, and even though clinical and laboratory investigations may suggest obvious causes, a definite diagnosis may require a kidney biopsy.

Case presentation

A 45 year old Caucasian male was admitted to the nephrology department because of declining renal function. He was in good clinical condition, afebrile, with a blood pressure of 145/90 mmHg and a regular pulse of 90 beats per minute. Oxygen saturation was 97% on pulse oximetry while breathing ambient air. He had no rash, oedema or arthritis. Clinical examination was remarkable for a recent thoracotomy scar over his left hemithorax without signs of infection. He was not oliguric and urinalysis showed 1+ protein, 5-
10 leucocytes/HPF and 65-70 red blood cells/HPF, with scant red blood cell casts. Proteinuria was 1.6 g/24h. Urine culture was sterile. Serum urea was 104 mg/dl and serum creatine 4.7 mg/dl. Electrolytes and liver function tests were normal. His full blood count showed WBC: 9100/μl (normal differential), PLTs: 414000/μl and haemoglobin 8.4 g/dl, MCV 74fL, MCH 24 pg, with a ferritin of 736 ng/ml (normal range 21.8-274.7 ng/ml). ESR was 85mm/1st hr and CRP 2.08 mg/dl (normal levels <0.8 mg/dl). ANA titter was positive at 1/160 (thin speckled pattern). ANCA, antiMPO, antiPR3 and anti-GBM were negative. Kidneys were normal on ultrasound.

He had a 3 year history of malignant pleural mesothelioma, initially treated by surgical excision, and followed by a 6 month course of chemotherapy with cisplatin and pemetrexed. Four months before admission the tumor relapsed and he was treated again by surgical excision. This was complicated by wound dehiscence due to Staphylococcus aureus infection, successfully treated with teicoplanin and linezolid. One month before admission he received one cycle of carboplatin and pemetrexed. Doses were adjusted to decreased renal function, because of a newly elevated creatinine at 1.7 mg/dl. On routine evaluation before the second chemotherapy cycle his creatinine had further increased to 4.7 mg/dl and he was transferred to the nephrology department. He had a 2 year history of well controlled hypertension on irbesartan. He was a non-smoker, social drinker and did not report any illicit drug use.

On the second day of admission and despite intravenous hydration his creatinine had reached 6.0 mg/dl. For presumed drug related acute interstitial nephritis he received 3 daily intravenous pulses of 500 mg methylprednisolone followed by oral administration of 48mg methylprednisolone od, with good response. He was discharged 5 days later with a creatinine of 3.5 mg/dl. After one week he still had microhematuria with decreasing creatinine at 2.8 mg/dl. Two weeks after fast steroid tapering, while on 16mg oral methylprednisolone, his creatinine rose up again to 4.0 mg/dl (Figure 1). A renal biopsy was performed.

The sample contained 26 glomeruli, one of which was obsolete, 2 showed focal fibrinoid necrosis and 9 showed extracapillary hypercellularity, in the form of two cellular and seven fibrocellular crescents (Figure 2). Uninvolved glomeruli were unremarkable. There was mild acute tubular injury and focal, mainly mononuclear interstitial inflammatory infiltration. Tubular atrophy and interstitial fibrosis were about 5% of the cortical area. There was no evidence of necrotizing arteritis. Immunofluorescence was negative for immunoglobulins or complement. Electron microscopy was not performed. Findings were consistent with pauci-immune necrotizing crescentic glomerulonephritis.

The patient was treated with oral cyclophosphamide (50 mg od, at 0.75 mg/kg) and 48 mg methylprednisolone od on slow taper. After a week

**Figure 1.** Serum creatinine (SCr) levels, events and interventions during the patient’s course.
his creatinine started to decline gradually, reaching 1.7 mg/dl after four months. At six months cyclophosphamide was switched to oral azathioprine 50mg bd and methylprednisolone was maintained at 4mg od. Two years after the biopsy, still on azathioprine and steroids, his urinalysis is normal and his creatinine is stable at 1.2 mg/dl (CKD-EPI eGFR: 71.6 ml/min/1.73m²), even though he received a 6 month chemotherapy course with carboplatin and pemetrexed for relapsed mesothelioma (Figure 1).

Discussion

We describe an extraordinary case of ANCA(-) pauci-immune necrotizing crescentic glomerulonephritis presenting with rapidly declining renal function, haematuria and non-nephrotic proteinuria, in a patient with relapsing malignant pleural mesothelioma initially treated by excision, which was complicated by wound dehiscence due to staphylococcus aureus infection, followed by chemotherapy with carboplatin and pemetrexed.

The causes of rapid renal function loss in oncology patients on chemotherapy may be prerenal, such as volume depletion from vomiting and diarrhoea, or renal, including tubular and interstitial injury due to sepsis, myeloma casts, tumor lysis syndrome, or toxicity from chemotherapeutic medications. Glomerular causes are less frequent and include thrombotic microangiopathy, which may be paraneoplastic or related to antineoplastic agents, mainly calcineurin inhibitors, mTOR inhibitors and anti-angiogenetic treatments. Rarely necrotizing crescentic glomerulonephritis may be the cause of rapid renal function decline.

In the patient described, renal function started to decline after staphylococcal wound infection despite good response to treatment with teicoplanin and linezolid, and continued to deteriorate despite adequate hydration. The presence of non-nephrotic proteinuria and microhematuria with scant red blood cell casts suggested renal parenchymal injury but could not differentiate between glomerular and tubulointerstitial causes, especially in the absence of ANCA positivity and lack of eosinophiluria, eosinophilia or extrarenal manifestations, such as fever or rash. However, drugs are the most frequent cause of acute tubulointerstitial nephritis, which has been described previously both with pemetrexed and, more rarely, with carboplatin. Thus, based on the patient’s history it was at first decided to treat him as acute tubulointerstitial nephritis with steroids. Despite good initial response, there was a relapse during fast steroid tapering. A renal biopsy was required to establish a definite diagnosis.

The findings of pauci-immune necrotizing crescentic glomerulonephritis were rather unexpected and required clinicopathological correlation. ANCA associated vasculitis has been occasionally reported in association with malignancies, most often solid tumours such as renal, gastric or lung cancers. Paraneoplastic pathogenetic mechanisms remain unknown. Treatment with cyclophosphamide and steroids in addition to tumor removal has been effective, but there is currently no evidence of vasculitis response to anti-cancer treatment alone. There are case reports of malignant mesothelioma in association with membranous nephropathy, minimal change disease, IgA nephropathy, Henoch-Schoenlein purpura, membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis, but to our best knowledge this is the first report of pauci-immune crescentic glomerulonephritis coinciding with malignant mesothelioma. Despite tumor relapse that had to be treated with chemotherapy, renal disease remained in remission, while on maintenance treatment with azathioprine and mini-
mal steroid dose. Even though a causative association between malignant pleural mesothelioma and glomerulonephritis cannot be verified, an accurate diagnosis is crucial for effective treatment.

About 10-30% of patients with pauci-immune crescentic glomerulonephritis are ANCA negative\(^4\). These cases are still considered as ANCA-related vasculitis and may result from ANCA(-) cases that are not detectable by routine methods, or vascular injury may be caused by ANCA independent mechanisms, possibly also associated with neutrophil involvement\(^5\). In cancer patients ANCA(-) renal vasculitis has been reported in association with nonsmall cell lung cancer\(^6,7\) and with endometrial neuroendocrine small cell carcinoma\(^8\). Lacking controlled prospective studies in patients with ANCA(-) vasculitis, treatment protocols are similar to those for ANCA(+) patients, although renal outcomes appear less favorable in ANCA(-) cases\(^4\).

Also relevant to the presented case, ANCA(-) renal vasculitis was described in a patient with Staphylococcus aureus diskitis, responding favourably to successful antibiotic treatment only\(^9\). Staphylococcus aureus infection has been associated with granulomatosis with polyangiitis (Wegener’s)\(^10\) and PR3(+) small vessel vasculitis\(^11\). Infective endocarditis, mainly staphylococcal and streptococcal, has also been associated with ANCA(-) pauci immune necrotizing crescentic glomerulonephritis\(^12\). Our patient had no evidence of active infection on admission and ANCA(-) vasculitis was described in a patient with Staphylococcus aureus diskitis, responding favourably to successful antibiotic treatment only\(^9\). Staphylococcus aureus infection has been associated with granulomatosis with polyangiitis (Wegener’s)\(^10\) and PR3(+) small vessel vasculitis\(^11\). Infective endocarditis, mainly staphylococcal and streptococcal, has also been associated with ANCA(-) pauci immune necrotizing crescentic glomerulonephritis\(^12\). Our patient had no evidence of active infection on admission and ANCA(-) vasculitis was persistently negative. There was no infectious exacerbation or complication with immunosuppression, so the association of renal vasculitis due to active staphylococcal infection seems rather unlikely.

Our case reports the unexpected coincidence of ANCA(-) pauci-immune necrotizing crescentic glomerulonephritis with malignant pleural mesothelioma, not previously described. It also emphasizes on the diagnostic importance of a renal biopsy in the evaluation of renal function decline in oncology patients. Our unexpected results had to be interpreted in respect to patient’s complex clinical history, in order to provide effective treatment with a favorable renal outcome.

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**Conflict of interest**

The authors declare that they have no relevant conflict of interests.
Βιβλιογραφία


