AP-VAS 2012 case report: a case of ANCA-negative pauci-immune crescentic glomerulonephritis associated with IL-6-producing adenosquamous cell carcinoma of the lung

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Received: 4 September 2012 / Accepted: 7 January 2013 / Published online: 14 March 2013
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Abstract A 76-year-old man with lung cancer and multiple metastases was admitted for purpura and rapidly progressive glomerulonephritis. Adenosquamous cell carcinoma of the lung had been diagnosed 6 months earlier. Two anti-cancer drug regimens had no effect. At admission, his survival with his malignancy was estimated to be several months. Renal biopsy revealed pauci-immune necrotizing crescentic glomerulonephritis (CrGN). Negative results were obtained for myeloperoxidase-anti-neutrophil cytoplasmic antibody (ANCA) and proteinase-3-ANCA by enzyme-linked immunosorbent assay, and for peripheral-ANCA and cytoplasmic-ANCA by indirect immunofluorescence. He was diagnosed with ANCA-negative pauci-immune CrGN. Although steroids were initiated, the patient died of renal failure and intestinal bleeding 2 weeks later. It was later found that cancer cells were positive for interleukin (IL)-6 and that serum IL-6 levels were significantly elevated, concomitantly with increased IL-8, granulocyte-colony stimulating factor and transforming growth factor- β levels. Some kinds of lung cancer are known to produce IL-6 that activate neutrophils and are related to

ANCA-associated CrGN. It appears that IL-6 can activate neutrophils in the pathogenesis of ANCA-negative pauci-immune CrGN with lung cancer. Therapy that blocks IL-6 may prove to be effective in vasculitis and cancer-related symptoms in such cases.

Keywords ANCA-negative crescentic glomerulonephritis · Interleukin-6 · Neutrophil · Lung cancer

Introduction

Crescentic glomerulonephritis (CrGN) is a morphologic expression of severe glomerular injury that usually correlates clinically with rapidly progressive glomerulonephritis (RPGN) [1, 2]. Pauci-immune CrGN is one of the most common types of CrGN, characterized by focal necrotizing glomerulonephritis with little or no glomerular staining for immunoglobulin or complement [1, 2]. Most patients with pauci-immune CrGN have anti-neutrophil cytoplasmic antibodies (ANCAs) in the circulation, so-called ANCA-associated CrGN [2]. However, some patients with this form of glomerulonephritis have no ANCAs [3–6]. The pathogenesis of ANCA-negative pauci-immune CrGN has not been fully clarified [4].

Interleukin (IL)-6 is a pleiotropic cytokine that has pivotal roles in the regulation of the immune response, inflammation, and hematopoiesis. Deregulated IL-6 levels are associated with various immunological diseases, such as rheumatoid arthritis and Castleman's disease [7]. In ANCA-associated CrGN, IL-6 plays an important role in the activation of neutrophils, which is attributed to the induction of IL-17-producing helper T cells [8]. While ANCA-negative CrGN may be considered an independent

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disease entity from ANCA-associated CrGN [4], there should be a common pathway for the development of vasculitis in both diseases. It is possible that neutrophils and their activation by IL-6 together with several cytokines play a crucial role in the pathogenesis of ANCA-negative, as well as ANCA-positive, CrGN. Conversely, some kinds of lung cancer are known to produce IL-6 [9–11]. In these IL-6-producing cancers, IL-6 plays a pivotal role in paraneoplastic manifestations, such as fever, general fatigue, and anemia [10, 11]. To our knowledge, we present here the first case report of a patient with ANCA-negative pauci-immune CrGN with IL-6-producing adenosquamous cell carcinoma of the lung.

Case report

A 76-year-old man was found to have a right lower lung tumor on chest X-ray and was referred for transbronchial lung biopsy in February 2010. The results of that examination showed adenosquamous cell carcinoma. Fluorodeoxyglucose-positron emission tomography (FDP-PET) revealed that the lung tumor was 10 cm in length and that there were multiple metastases in the right hilar and paratracheal lymph nodes, liver, and peritoneum (Fig. 1). He was diagnosed as having adenosquamous cell lung cancer with multiple metastases (T3N2M1b) and was

treated with the first-line regimen of carboplatin [target area under the concentration versus time curve (AUC) = 5 mg/mL/min] and paclitaxel from March to May. Because the tumor increased in size despite this treatment, the second-line regimen of docetaxel was started in June; however, this was also ineffective. Since his predicted survival with the malignancy was several months, best supportive care was provided, including 10 mg/day prednisolone for tumor fever from July onwards. In the beginning of August, he developed purpura and slight edema on the extremities. At that time, his kidney function was almost normal, with a serum creatinine of 0.8 mg/dL. At the end of August, he was admitted to our hospital because of RPGN.

On admission, his blood pressure was 150/70 mmHg, and his temperature was 36.8 °C on prednisolone at 10 mg/day for tumor fever. Systemic edema and extremity purpura were noted. Urinalysis showed 2+ protein and 3+ occult blood (Table 1). Urinary protein was 3.1 g/day, and creatinine clearance was 12.6 mL/min/1.73 m². Hematologic studies showed an increased white blood cell count, especially neutrophils, and anemia. Laboratory work-up showed renal failure, hypoproteinaemia, and an inflammatory reaction. Tests for antinuclear antibody and anti-GBM antibody were negative, as were tests for myeloperoxidase (MPO)-ANCA and proteinase-3 (PR3)-ANCA by enzyme-linked immunosorbent assay

Fig. 1 **a** Chest X-ray shows the right lower lung tumor, **b**, **c** fluorodeoxyglucose-positron emission tomography image shows increased uptake of the right lower lung, right hilar and paratracheal lymph nodes, liver, and peritoneum

Table 1 Laboratory data on admission

Laboratory tests	Values	Laboratory tests (continued)	Values
Urinalysis		Total protein (g/dL)	5.9
Specific gravity	1.014	Albumin (g/dL)	2.2
pH	5.5	Blood urea nitrogen (mg/dL)	65.2
Protein	2+	Creatinine (mg/dL)	3.3
Glucose	(–)	Sodium (mEq/L)	142
Occult blood	3+	Potassium (mEq/L)	3.8
β2-microglobulin (μg/L)	200	Chloride (mEq/L)	104
Urine sediment		Calcium (mg/dL)	8.2
Erythrocytes (dysmorphic) (/HPF)	≤100	Glucose (mg/dL)	156
Leukocytes (/HPF)	≤5–9	C-reactive protein (mg/dL)	10.4
Cast	Negative	HBsAg	(–)
Collection of urine		HCV	(–)
Daily proteinuria (g/day)	3.1	Immunology	
Creatinine clearance (mL/min/1.73 m ²)	12.6	Immunoglobulin G (mg/dL)	1156
Complete blood count		Immunoglobulin A (mg/dL)	546
White blood cell (/μL)	18,500	Immunoglobulin M (mg/dL)	20
Neutrophils (%)	92.0	Complement 3 (mg/dL)	75.6
Lymphocytes (%)	5.0	Complement 4 (mg/dL)	23.8
Monocytes (%)	2.0	Rheumatoid factor (IU/mL)	0
Eosinophils (%)	1.0	Cryoglobulin	(–)
Red blood cells (/μL)	294 × 10 ⁴	Antinuclear antibody	<40
Hemoglobin (g/dL)	8.8	Anti-GBM antibody	(–)
Hematocrit (%)	26.7	MPO-ANCA	<1.3
Platelets (/μL)	18.8 × 10 ⁴	PR3-ANCA	<3.5
Chemistry and infection		P-ANCA (IIF)	(–)
Aspartate aminotransferase (IU/L)	33	C-ANCA (IIF)	(–)
Alanine aminotransferase (IU/L)	13		
Alkaline phosphatase (IU/L)	492		
Lactate dehydrogenase (IU/L)	292		
Choline esterase (IU/L)	90		
Total bilirubin (mg/dL)	0.8		

HBsAg Hepatitis B virus surface antigen, HCV hepatitis C virus antibody, GBM glomerular basement membrane, MPO-ANCA myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA proteinase-3-ANCA, P-ANCA peripheral-ANCA, C-ANCA cytoplasmic-ANCA, IIF immunofluorescence

and for peripheral (P)-ANCA and cytoplasmic (C)-ANCA by indirect immunofluorescence.

A percutaneous renal biopsy was performed to diagnose and treat RPGN to prevent death from renal failure within a few weeks, although his prognosis related to lung cancer was estimated to be only several months. Histopathological examination revealed crescents in seven of 13 glomeruli (>50 %) (Fig. 2); five (71 %) were cellular and two (29 %) were fibrocellular. Necrotizing lesions with neutrophils were observed in most of the glomerular crescentic lesions, and two of 13 glomeruli were obsolescent. Most of the glomeruli had severe mesangial cell proliferation and endocapillary infiltration of a large number of neutrophils and monocytes. Focal tubulointerstitial inflammation with monocytes, fibrosis, and tubular atrophy were observed. Necrotizing or granulomatous vasculitis was not observed in the arteries. On immunofluorescence studies, slight deposition of immunoglobulin (Ig)A, C3, and fibrinogen

was observed, while IgG and IgM were absent. Electron microscopy did not show immune complex deposition. The diagnosis was ANCA-negative pauci-immune CrGN with lung cancer. Although methylprednisolone pulse therapy (500 mg/day × 3 days) was given, with a maintenance dose of 50 mg/day prednisolone, renal function continued to deteriorate. Moreover, intestinal bleeding developed, and he died 12 days after admission.

Immunohistochemical staining of the lung cancer tissue that had been obtained by transbronchial lung biopsy was later performed with an anti-human IL-6 rabbit polyclonal antibody (Rockland, Gilbertsville, PA) and an anti-human granulocyte-colony stimulating factor (G-CSF) mouse monoclonal antibody (Seikagaku Corp, Tokyo, Japan). Staining was positive for IL-6 and negative for G-CSF in the lung cancer cells (Fig. 3). Investigation of several cytokines was subsequently performed. Serum IL-6 levels were significantly elevated to 425 pg/mL (Table 2).

Fig. 2 Light microscopic findings of the renal biopsy [a, b Periodic acid-Schiff (PAS) stain, c Masson stain; a $\times 200$, b, c $\times 600$]. Crescent formations are present in $>50\%$ of observed glomeruli, and there is intensive proliferation of mesangial cells and endothelial cells with neutrophil infiltration. Tubulointerstitial inflammation with monocytes is observed (PAS stain). Fibrinoid necrosis (red) is observed in the crescentic lesion (Masson stain)

Fig. 3 Immunohistochemical staining of lung cancer with interleukin (IL)-6 polyclonal antibody (a, b $\times 200$, c $\times 600$) and granulocyte-colony stimulating factor (G-CSF) monoclonal antibody (d $\times 200$). Cancer cells are seen to be positive for IL-6 and negative for G-CSF

Table 2 Results of proinflammatory cytokines

Cytokines	Test value	Normal value
IL-1 β (pg/mL)	2.37	<0.928
IL-4 (pg/mL)	<0.5	<3.0
IL-6 (pg/mL)	425	<2.41
IL-8 (pg/mL)	121	<8.0
IL-10 (pg/mL)	8.17	<7.05
IL-17 (pg/mL)	<31.2	<31.2
TNF- α (pg/mL)	3.74	<1.79
INF- γ (pg/mL)	6.01	<20.6
G-CSF (pg/mL)	265	10.5–57.5
TGF- β (ng/mL)	41.7	0.89–1.8

IL Interleukin, TNF- α tumor necrosis factor- α , INF- γ interferon- γ , G-CSF granulocyte-colony stimulating factor, TGF- β transforming growth factor- β

Plasma IL-8, G-CSF, and transforming growth factor- β (TGF- β) levels were also significantly elevated. Other cytokine levels were slightly elevated or in the normal range.

Discussion

Crescentic glomerulonephritis is the most severe structural phenotype in the continuum of injury that results from glomerular inflammation [1, 2]. Due to severe glomerular injury, CrGN usually correlates with RPGN clinically [1, 2]. CrGN is classified into three main categories on the basis of direct immunofluorescence microscopic observations, i.e., an anti-GBM CrGN, an immune complex-mediated CrGN, and a pauci-immune CrGN that presents as focal necrotizing glomerulonephritis with little or no glomerular staining for immunoglobulin or complement [2]. Most patients with pauci-immune CrGN are seropositive for ANCA and are therefore known as ANCA-associated CrGN [2]. ANCA also plays a crucial role in the initiation and progression of ANCA-associated CrGN, but a significant number patients with pauci-immune CrGN are negative for ANCA.

ANCA-negative pauci-immune CrGN has been demonstrated in only a limited number of case reports [3–6]. The prevalence of this disease is approximately 10–30 % [3, 4]. From the perspective of clinical features, ANCA-negative patients are much younger and have fewer constitutional symptoms, including fever and arthralgia, than ANCA-positive patients [4]. ANCA-negative patients also have a higher prevalence of nephrotic syndrome and poorer renal survival than ANCA-positive patients. The pathogenesis of ANCA-negative pauci-immune CrGN remains unclear [4], but it has been speculated that there should be a common pathway leading to vasculitis in patients with

ANCA-positive or ANCA-negative CrGN [4]. Neutrophils are considered to play a major role in the pathogenesis of ANCA-negative pauci-immune CrGN [3, 4]. In addition, processes involved in the activation of neutrophils are thought to be important via antibodies other than ANCAs and via cell-mediated immunity; IL-17-producing helper T (Th17) cells induced by IL-6 together with transforming growth factor- β (TGF- β) could lead to neutrophil activation via the release of IL-8 [4, 12], a chemotactic ligand for neutrophils [13]. In the present case, there was infiltration of the glomerulus by a large number of neutrophils together with crescent formation. Moreover, serum IL-6 levels were significantly elevated in combination with significant increases in plasma TGF- β and IL-8 levels.

IL-6 is a pleiotropic cytokine that has pivotal roles in the regulation of the immune response, inflammation, and hematopoiesis [7]. Disruption of IL-6 regulation might induce immune-mediated inflammatory diseases, such as rheumatoid arthritis and Castleman's disease. The relationship between IL-6 and ANCA-associated vasculitis has been investigated in a number of clinical reports [14, 15]. Arimura et al. found that the serum IL-6 level increased in parallel with MPO-ANCA titers in patients with MPO-ANCA-associated CrGN, although it decreased during remission [14]. Ohlsson et al. [15] found that plasma IL-6 levels were significantly elevated in patients with ANCA-associated vasculitis in the active phase, heralding a greater risk of relapse. Moreover, the pathogenic role of neutrophils and IL-6 in ANCA-associated vasculitis has been gradually clarified [8, 16]. Hong et al. found that MPO-ANCA and PR3-ANCA isolated from patients with vasculitis induced the release of neutrophil microparticles, which then bound endothelial cells and induced IL-6 and IL-8 release [16]. Furthermore, IL-6 has been found to induce the generation of Th17 cells from naïve T cells, together with TGF- β [8, 12]. In a mouse study, Th17 cells were observed to play a role in the pathogenesis of experimental anti-MPO glomerulonephritis by neutrophil accumulation in the kidney that is dependent on IL-8 and IL-17 [17]. In a human study, there was an increased percentage of Th17 cells in the periphery, and serum IL-17 levels were elevated in acute ANCA-associated vasculitis patients [18]. In brief, IL-6 may play an important role in leading to neutrophil activation, together with IL-8 and IL-17, in the pathogenesis of ANCA-associated vasculitis.

In contrast to ANCA-associated vasculitis, neutrophil activation with IL-6 has rarely been reported in the pathogenesis of ANCA-negative CrGN. Shimizu et al. [5] observed neutrophil infiltration in the glomerular lesion and elevated IL-6 and IL-8 levels in the acute phase of ANCA-negative CrGN. Moreover, there have been a few reports of Th17 cells and IL-17 in patients with ANCA-negative CrGN. Abdulhad et al. observed a significant

increase in the percentage of Th17 cells in ANCA-negative Wegener's granulomatosis patients [19]. In our case, there was a large amount of neutrophil infiltration in the glomerulus, with crescent formation, and significant elevated levels of IL-6, TGF- β , and IL-8 in the blood, but serum IL-17 levels were in the normal range. Th17 cell counts in the periphery and renal tissue and IL-17 expression in the renal tissue were not evaluated. Nogueira et al. observed that 36 % of acute phase ANCA-associated vasculitis cases had serum levels of IL-17 in the normal range [18]. There are not a few rheumatoid arthritis and multiple myeloma patients with normal range serum IL-17 levels, in which Th17 and IL-17 are associated with their pathogenesis [20, 21]. It is therefore possible that there may be a discrepancy in IL-17 levels between blood and local inflammatory tissues. Conversely, in the present case, plasma INF- γ levels associated with Th1 and plasma IL-4 levels associated with Th2 were also in the normal range. Therefore, IL-6 may play a pathogenic role not with helper T cells but with other cytokines, such as IL-8 and G-CSF, that activate neutrophils. Further clinical studies are needed to confirm the roles of IL-6 in the pathogenesis of ANCA-negative pauci-immune CrGN.

IL-6-producing lung cancer has recently been reported in several cases. In one study, of 227 patients with lung cancer followed for over 7 years, three were diagnosed with IL-6-producing adenocarcinoma [9]. There are two case reports of IL-6-producing giant cell carcinomas of the lung [10, 11]. Independently of the cancer types, these patients had systemic manifestations, such as fever and general fatigue, as well as laboratory abnormalities, such as leukocytosis, anemia, thrombocytosis, hypergammaglobulinemia, and elevated C-reactive protein levels because of IL-6 [9–11]. Our patient had most of these features without thrombocytosis and hypergammaglobulinemia. The reasons for these distinctions may be attributed to bone marrow depression by two anti-cancer drug regimens and nephrotic range proteinuria. On the other hand, vasculitis was not seen in previous cases. Activated neutrophils and elevations of other cytokines, such as IL-8 and G-CSF, may have resulted in the renal complications of our patient.

A humanized anti-IL-6 receptor antibody, tocilizumab, has been demonstrated to be effective for several types of vasculitis [22, 23]. Moreover, in MPO-ANCA-associated CrGN complicated with rheumatoid arthritis, this antibody improves the symptoms of both rheumatoid arthritis and CrGN [24]. On the other hand, anti-IL-6 agents could provide a novel therapeutic strategy in patients with IL-6-producing lung cancer. IL-6 produced by cancer cells has been found to play a pivotal role in paraneoplastic manifestations, such as fever, general fatigue, and anemia [10, 11]. In a mouse model, development of cancer-related anemia was prevented with the administration of rat anti-

mouse IL-6 receptor antibody [25]. In humans, humanized anti-IL-6 antibody ameliorated lung cancer-related anemia and cachexia [26]. Therapy that blocks IL-6 might be effective for vasculitis and cancer-related symptoms in cases such as the present one.

Acknowledgments The authors would like to thank Nozomi Tuji, PhD for scientific and technical advice.

Conflict of interest The authors have declared that no conflict of interest exists.

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