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Invasive adenocarcinoma of the lung associated with membrano-proliferative glomerulonephritis and myeloperoxidase anti-neutrophil cytoplasmic antibody

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Introduction

Paraneoplastic nephrotic syndrome is known to be associated with malignancies such as lung cancer, prostate cancer, lymphoma and colonic cancer. Of them, lung carcinomas are notoriously known for being associated with paraneoplastic nephrotic syndrome. The most common glomerulonephritis variants associated with lung carcinomas are minimal change disease (MCD) and membranous nephropathy. Membranoproliferative glomerulo--nephritis (MPGN) association is very rarely reported in the literature.

Nephrotic syndrome refers to a constellation of clinical and laboratory features of kidney disease. It is defined by the presence of urinary protein excretion greater than 3.5 g/24 hours along with hypoalbuminemia (less than 3.5 g/dL) and peripheral oedema. Isolated heavy proteinuria without overt oedema or other features of nephrotic syndrome is suggestive of glomerulopathy. Isolated heavy proteinuria is not necessarily associated with hyperlipidemia and thrombotic diseases as in classic nephrotic syndrome. Heavy proteinuria with or without nephrotic syndrome can manifest due to primary or systemic (secondary) disease conditions (1). In adults, primary renal diseases are MCD, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy and other cases are secondary to diabetes mellitus, amyloidosis, or systemic lupus erythematosus (1).

Anti-neutrophil cytoplasmic antibodies (ANCAs) are autoantibodies produced by the immune system, which mistakenly target and attack proteins within an individual's neutrophils. ANCA association with solid organ malignancies without underlying vasculitis is been reported (2).

We describe a young man who presented with nephrotic range proteinuria later found to have underlying adenocarcinoma of the lung, co-existing MPGN, and MPO anti-neutrophil cytoplasmic antibody (pANCA).

Case presentation

A 39-year-old previously healthy ex-smoker, presented with a cough, weight loss of 17 kilograms, and loss of appetite for four months duration. He had a non-productive cough, associated with progressively worsening exertional shortness of breath. But he denied heart failure symptoms, hemoptysis, personal or contact history of TB, and contact history of novel coronavirus. No associated nasal or ear discharge, nasal congestion, or nasal crusting. His urine output was satisfactory and he had noticed froth in urine for the past five months without nocturia or hematuria. The patient denied morning stiffness, any connective tissue disease features, or any high-risk behaviour.

Physical examination revealed elevated blood pressure (BP) of 160/100 mmHg without postural

variation. No overt feature of fluid overload. The trachea was deviated to the right side. There was a hard lymph node on the left anterior cervical group. The rest of the examination findings were normal. His chest X-ray showed right hilar mass with ipsilateral volume impairment (Figure 1). Non contrast high resolution CT (HRCT) chest showed right side perihilar inflammatory consolidations associated with pneumonitis / alveolitis and early fibrosis without mediastinal adenopathy. This was followed by contrast computed tomography (CECT) which revealed bilateral patchy consolidation, perihilar interlobular septal thickening, peribronchovascular soft tissue thickening, small cyst formation, and mediastinal lymphadenopathy.

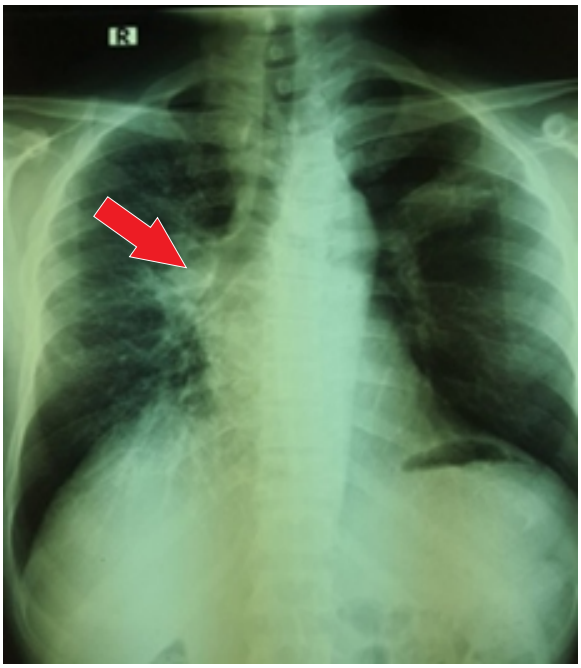

Figure 1: Chest X-ray with right hilar mass (red arrow) and ipsilateral volume impairment

His laboratory work-up showed leukocytosis with predominant neutrophils, normochromic normocytic anemia, and normal platelet count. Erythrocyte sedimentation ratio was 58 mm/1st hour and C reactive protein was 10 mg/dL. Urine analysis revealed proteinuria without active sediment. Twenty four-hour urine quantification revealed nephrotic range proteinuria (9,339 mg/24-hour). Serum albumin was 29 g/L, but total serum cholesterol was 80 mg/dL. Dysmorphic red cells were not detected in urine.

His autoimmune panel was positive for MPO antibody (pANCA) and the rest of the immune markers were negative including ANA and cANCA. Anti-GBM antibody was not available during the time of management. Screening for retroviral infections and syphilis were negative. Renal functions were elevated with creatinine of 199 µmol/L and blood urea of 38.5 mmol/L. Renal ultrasonography showed increased cortical echogenicity and prominent pyramids indicating chronic renal parenchymal disease.

Flexible bronchoscopy showed narrowing of the right medial lobe bronchus with contact bleeding and narrowing at the lingular lobe opening with contact bleeding. Bronchial wash cytology and brush cytology had atypical cells but were not significant enough to conclude a diagnosis. Broncho-alveolar lavage for silver staining and viral antibody panel were negative. All the workups for tuberculosis were normal.

Renal biopsy revealed 8 out of 12 viable glomeruli with a membranoproliferative pattern of injury with immunofluorescence strong positivity (3+) for IgG and moderate positivity (1+) for IgA and IgM. Appearances with immunofluorescence are consistent with an immune complex-mediated membranoproliferative glomerular nephritis (MPGN) (Figure 2).

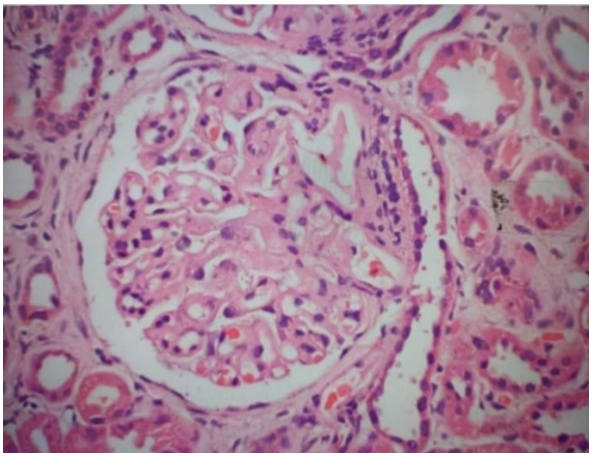

Figure 2: Histological features suggestive of membranoproliferative glomerulonephritis

At the outset, our working differential diagnosis was carcinoma of the lung with immune complex-mediated MPGN, anti-GBM disease, or ANCA-

associated vasculitis such as granulomatosis polyangiitis (GPA) or microscopic polyangiitis (MPA). With multi-disciplinary team discussion (MDT) with nephrology and respiratory physician, IV methylprednisolone pulse therapy followed by high-dose oral glucocorticoid treatment was commenced. Meanwhile, his cervical lymph node biopsy revealed a metastatic adenocarcinoma with a lepidic pattern with possible primary lung malignancy. A more favourable diagnosis was primary lung adenocarcinoma with paraneoplastic MPGN with associated with pANCA. Since the patient did not show any improvement with immunosuppression, glucocorticoid treatment was withheld. Following the second MDT discussion, the patient was referred to oncology for further treatment. However, while on chemotherapy patient succumbed to lung cancer.

Discussion

Solid tumours are well known to be associated with the nephrotic syndrome (NS). Sometimes lung cancers can be heralded by NS. MGN is the most common NS in adults related to lung tumours; the association with MPGN is uncommon (3).

MPGN is a disease defined by a pattern of glomerular injury observed by light microscopy on renal biopsy and three types have been described according to the histology. There are two distinct presentations of MPGN. Presentation in childhood is common with nephritic pictures and is mostly idiopathic in origin. In contrast, adults present with nephrotic range proteinuria, and histologically it is either type I or III (4). It is histologically characterised by mesangial hypercellularity, endocapillary proliferation, and double-contour formation along the glomerular capillary walls (5). Pathogenesis of MPGN can be idiopathic or secondary to immune complex deposition, and complement system activation. Immune complex-mediated MPGN pattern of injury may result from multiple causes including infection, autoimmune diseases, and monoclonal gammopathies. Idiopathic MPGN can be rarely associated with malignancies. Though MPGN in association with small cell lung cancer has been reported previously, primary lung adenocarcinoma causing paraneoplastic MPGN has not been described in the literature (6).

Anti-neutrophil cytoplasmic antibodies (ANCAs) are autoantibodies produced by the immune system, which mistakenly target and attack the proteins within an individual's neutrophils.

A wide variety of pulmonary abnormalities such as pulmonary fibrosis, pulmonary hemorrhages, and malignancies are known to be associated with myeloperoxidase (MPO) antibodies (7). MPO and proteinase-3 (PR3) antineutrophil cytoplasmic antibody (ANCA) associated crescentic glomerulonephritis (CGN) is a major cause of rapidly progressive glomerulonephritis (RPGN). ANCA-associated CGN is generally classified as pauci-immune RPGN, in which there are a few or no immune complexes. ANCA-associated vasculitis (AAV) is a rare, autoimmune disease with underlying inflammation of blood vessels. It causes multi-systemic manifestations including lung, paranasal sinuses, kidneys, neurons, etc. According to the involvement of the dominant system, AAV comprises granulomatosis with polyangitis (GPA), microscopic polyangitis (MPA), and eosinophilic granulomatous polyangitis (EGPA).

The relationship between AAV and lung malignancies remains unclear (8). However, granulomatosis with polyangitis has been sequentially detected in a patient who had been initially treated for adenocarcinoma of the lung (9). Another case has been reported with adenocarcinoma of the lung associated with a highly positive pANCA and clinical signs of microscopic polyangitis (10). Other case reports have described lung cancer preceding or coinciding with either IgA vasculitis, pauci-immune necrotizing crescentic glomerulonephritis, and sarcoidosis (11-13). They have described that vasculitis can be the first presentation of the malignancy or be detected with an average of two years latency to the primary lung cancer.

Our patient who had invasive adenocarcinoma of the lung, and initial nephrotic range proteinuria guided us to evaluate for renal-pulmonary syndromes. Though his MPO antibody was positive, he did not meet the clinical criteria to diagnose AAV. On further evaluation, his renal biopsy showed evidence of MPGN. Elevated serum MPO and PR3 antibody levels can be seen with lung adenocarcinoma without overt AAV. Once the

primary malignancy has been resected or malignancy-directed treatment is provided, autoantibody titres will be reduced (2).

Tatsis *et al.,* have evaluated the frequencies and types of malignancies occurring before or simultaneously with a diagnosis of positive PR3 ANCA (14). According to the above evaluation, the most common malignant disease was renal cell carcinoma. Only one patient had been described with co-existing lung cancer. Other than the presenting case, there are only a few such described cases in the literature.

Patients with cancer can present either with proteinuria or overt nephrotic syndrome due to an underlying malignancy, which is called paraneoplastic manifestation. Paraneoplastic nephrotic syndrome is generally associated with malignant lymphoma and other non-epithelial neoplasms (15). The most common glomerulonephritis associated with malignancy is membranous nephropathy (16). Although rare, MPGN can be associated with lung cancers (15, 17). The mechanism of developing renal disease with malignancy is an area of debate. There are several hypotheses to explain the pathophysiology of glomerulonephritis. Malignancy-associated antigen deposition can cause a GN as a paraneoplastic manifestation. Conversely, immunosuppressive medications used for glomerulonephritis itself may provoke tumour genesis (18). Treatment for MPGN is based on the underlying etiology. Most of the time it is immunosuppressive drugs that play a prominent role in treating MPGN (19). But interestingly immunosuppressive treatment has limited efficacy in achieving response. Though we have administered immunosuppressive therapy, our patient did not show any clinical or biochemical response. Even after treatment for lung carcinoma with chemotherapy, proteinuria and renal functions did not ameliorate.

Conclusions

Though it is extremely rare, invasive lung adenocarcinoma can be the underlying cause for paraneoplastic MPGN. Patients who have pulmonary and renal system involvement, clinicians should investigate to exclude underlying ANCA-associated vasculitis. Isolated high titers of MPO autoimmune antibody can be seen with primary lung adenocarcinomas without overt vasculitis. Therefore, it is prudent to consider urgent oncology treatment for possible of lung malignancy with MPGN rather treating for vasculitis.

Written informed consent was obtained from the relatives of the patient for publication of this case report and any accompanying images.

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