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2074 Words

CHARACTER COUNT

12477 Characters

PAGE COUNT

5 Pages

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600.5KB

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Secondary Glomerulonephritis due to Non-Hodgkin Lymphoma: Case Report and Literature Review

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Abstract
Glomerulonephritis is an inflammatory process in the glomerular region of the kidney with a clinical spectrum ranging from isolated asymptomatic proteinuria to nephrotic syndrome. The etiology of glomerulonephritis, either primary or secondary, must be determined at the start of the diagnostic process. A 21-year-old woman presented with swollen legs, slight shortness of breath, and a history of glomerulonephritis. Physical examination revealed venous distensions in the anterior neck and anterior thoracic regions. Laboratory results indicated proteinuria, hypoalbuminemia, and cholesterolemia. Further examinations indicated a suspicious right lung mass on a chest film, and computerized tomography showed a solid right lung mass staged as T4NxMx. The histopathology result was non-Hodgkin lymphoma, and the patient was diagnosed with secondary glomerulonephritis caused by malignancy. Primary therapy for secondary glomerulonephritis calls for cause management, so this involved chemotherapy for the non-Hodgkin lymphoma malignancy.
Keywords : glomerulonephritis, malignancy, non-Hodgkin lymphoma

Introduction

Based on etiology, glomerulonephritis can be designated as either primary (i.e., idiopathic) or secondary. The causes of primary glomerulonephritis are limited to within the kidney, and although their etiologies are unknown, they are considered to be related to both genetics and immunology. In contrast, secondary nephrotic syndrome can result from infections, malignancies, connective tissue diseases, drugs or toxins, and from systemic disease(1).
Patients with urine abnormalities, especially those with mild proteinuria, are often not evaluated for the possibility of secondary glomerulonephritis, especially the possibility of it being related to malignancy(2). Lee et al. found that 11% of glomerulonephritis patients also had a malignant disease, and lung tumors with subsequent gastrointestinal carcinomas have been reported to be the most common solid tumor malignancies that cause glomerulopathy disorders(3).

Here, we report the case of a woman with glomerulonephritis secondary to intrathoracic non-Hodgkin lymphoma with superior vena cava syndrome.

Case Presentation

A 21-year-old female patient presented with the chief complaint of shortness of breath which had worsened one week before her hospital admission. Three months before admission, the patient complained of swollen legs and consulted a physician. After an initial physical examination and laboratory findings, she was diagnosed with glomerulonephritis and needed to be worked up further. The patient stated she had never been given drugs such as methylprednisolone or prednisone, or any other medicines that required long-term use. The patient had only one follow-up visit with the physician, but was never returned.

Approximately three days before hospital admission, the patient felt shortness of breath which was not affected by activity level and did not increase when lying down. The patient's feet were slightly swollen, and her urine volume was sufficient (sometimes foamy but no red color), and she had no pain when urinating. The patient had no complaints about a neck lump, frequent sweating or shaking, any thyroid problem, frequent oral ulcers, hair loss, joint pain, and had no history of either facial redness from sun exposure or kidney disease as a child. The patient was single, a non-smoker (but her father was a heavy smoker), and possible chemical exposure was dismissed.

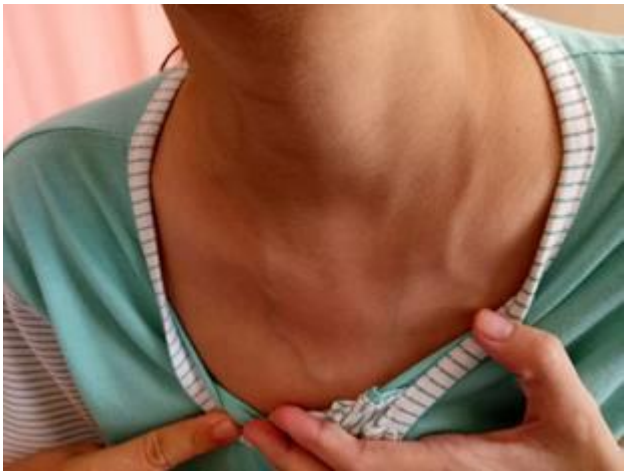

Figure 1: Venous distensions of the anterior chest and neck.

Physical examination revealed venous distensions of the anterior chest and neck (Figure 1). There was no thyroid enlargement, no enlargements of lymph nodes in the neck region, or in the supraclavicular, infraclavicular, axillary, or femoral regions. The pulmonary examination found decreased right-chest vesicular sounds, but crackles and wheezing were absent. There was right-chest percussive dullness. An examination of her extremities revealed mild edema.

Hospital laboratory values were: hemoglobin 10.6 g/dL, urea 27 mg/dL, creatinine 0.52 mg/dL, albumin 2.5 g/dL, total cholesterol of 272 mg/dL, LDL 233 mg/dL, HDL 18 mg/dL, and triglycerides 163 mg/dL. Urinalysis showed proteinuria +1 and 24-hr urine protein was 0.1 g/dL/day. An antinuclear antibody (ANA) test was negative. A chest film showed CTR < 50%, a tracheal shift to the left, a suspected mass in the right lung, and no infiltrates (Figure 2).

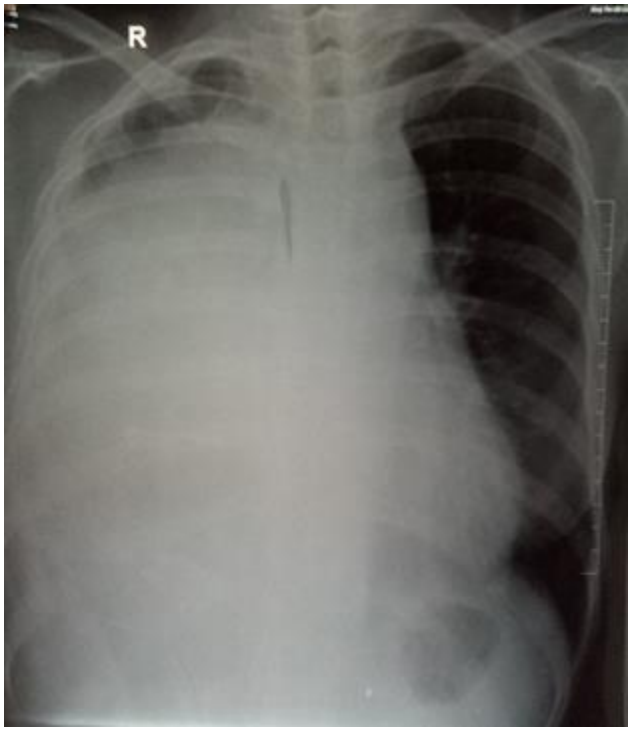

Figure 2: A chest film showing a suspected mass in the right lung.

Kidney and urinary tract ultrasonography showed both right and left kidneys: normal shape and size, no increased parenchymal intensities, clear cortical-medullary borders, no observed cysts/stones/nodules, and no

dilation of the pelvicalyceal system. The bladder was normal in shape and size with no observed mass or stones, and the uterus was normal in shape and size. Echocardiography showed normal wall motion, normal valves, normal LV systolic function, an ejection fraction of 60%, normal diastolic function, and minimal pericardial effusion. As an initial treatment, the patient was given oxygen for her shortness of breath, furosemide 2 × 40 mg, dexamethasone 3 × 5 mg, omeprazole 1 × 40 mg, and simvastatin 1 × 20 mg.

Chest computerized tomography (CT) showed that there was a mass in the right anterior lung, a good bronchovascular streak, and no visible infiltrates or metastatic nodules in both lung fields. The trachea, carina, right and left main bronchi, aortic arch and aorta were all normal, and no pleural effusions were observed. The heart was pushed to the left, the mediastinal and hilar lymph nodes did not appear enlarged, the adrenal glands were not enlarged, and bones appeared to be intact. The diagnostic impression from the CT was a right lung solid mass pushing the heart to the left with T4NxMx staging (Figure 3).

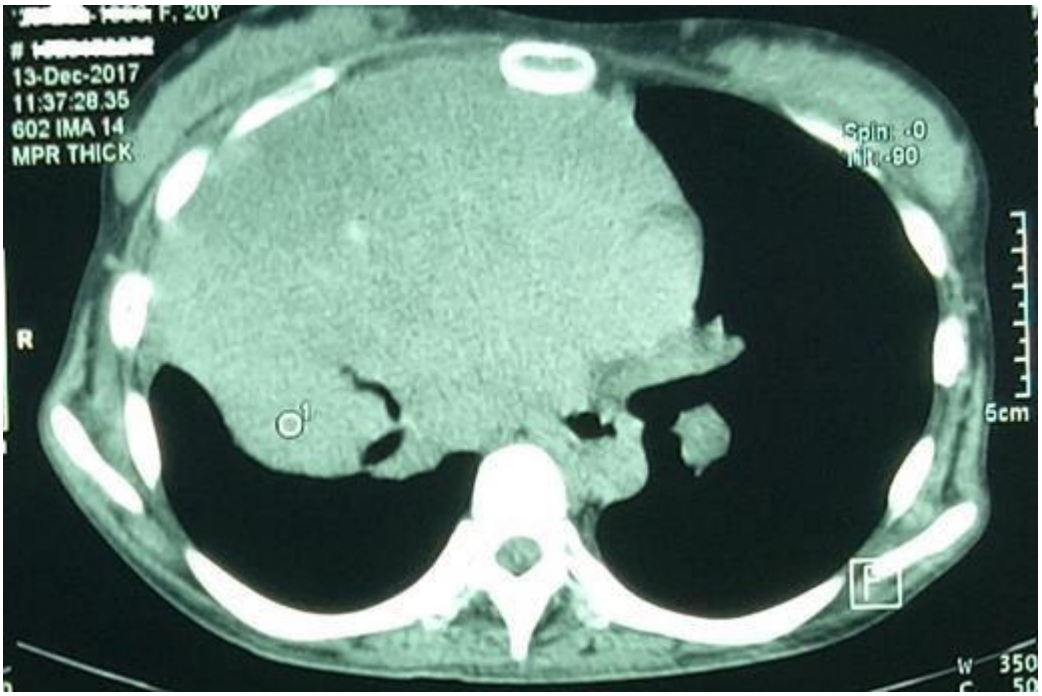

Figure 3: A thoracic CT image showing a right-lung solid mass.

A transthoracic biopsy was then performed, and the histopathology results indicated non-Hodgkin lymphoma. The patient then began CHOP regimen chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone), and her evaluation after chemotherapy cycling showed both tumor remission and the disappearance of the proteinuria.

Discussion

In general, the etiologies for glomerulonephritis are either primary or secondary. Primary (idiopathic) glomerulonephritis is associated with a cause intrinsic to the kidney and not associated with systemic disease. In contrast, secondary nephrotic syndrome is associated with causes extrinsic to the kidney, including autoimmune diseases (e.g., Henoch-Schonlein purpura and systemic lupus erythematosus), infectious diseases, malignancies, environmental chemical exposures and drugs, and systemic diseases (e.g., diabetes mellitus). The possibility of secondary glomerulonephritis resulting from an extrarenal cause should always be considered if a case of glomerulonephritis is encountered, including malignancy as a possible cause(1, 4).

For this patient, her complaints began with slightly swollen legs three months before admission, and the problem was diagnosed as glomerulonephritis. Unfortunately, the patient did not return to the diagnosing physician for treatment. The laboratory values indicated hypoalbuminemia, hypercholesterolemia, proteinuria (mild), and normal creatinine.

The patient had superior vena cava syndrome and a suspected right lung mass. This syndrome represents an obstruction of the superior vena cava due to internal or external compression that causes impaired return of blood to

the right atrium. The chest tightness suffered by patients is usually due to edema up to the larynx. Short-term dexamethasone has been administered to reduce larynx edema in this syndrome(5). The patient also had a pericardial effusion which was thought to be because of her hypoalbuminemia.

The CT evaluation identified a T4NxMx tumor, and this patient's risk factor (the father was a heavy smoker) was external. However, even though no other family members had such a tumor, it is possible that genetic factors may have contributed to its occurrence.

With the diagnosis of non-Hodgkin lymphoma malignancy, this patient's glomerulonephritis was designated as a secondary glomerulonephritis. No other causes for secondary glomerulonephritis were suspected, and the patient did not complain of hair loss, photosensitivity, or joint pain, and her ANA test was negative.

Malignant nephropathies have been known for a long time, with the most common associations being between solid tumors and nephrotic syndrome due to membranous nephropathy, and between Hodgkin's disease and minimal-change glomerulonephritis. The most common presentation is nephrotic syndrome, with approximately 40% of glomerulonephritis patients presenting before the diagnosis of malignancy is made(6, 7). The true incidence of glomerulopathy due to malignancy is unknown because patients with malignant disease often have mild urinary abnormalities and are rarely referred for treatment. Lee et al. reported that 11% of glomerulonephritis patients had malignancies(3).

The most commonly identified nephropathy is membranous glomerulonephritis, occurring in approximately 70% of patients diagnosed with malignancy-related glomerulonephritis. Its microscopic and ultra-structural appearance is similar to that of idiopathic membrane nephropathy(2). No kidney biopsy was performed in this patient because she refused it, but for isolated conditions of proteinuria within the non-nephrotic range, without hematuria, and with normal renal function, a kidney biopsy is not required. In addition, this patient also did not show signs of systemic disease conditions such as an autoimmune disorder or vasculitis that would have necessitated a kidney biopsy(8).

The four main mechanisms by which solid tumors can be associated with glomerulopathy include: (a) Antibodies may be formed against a tumor antigen identical to an endogenous podocyte antigen, leading to an *in situ* immune complex. (b) Shed tumor antigens may form circulating immune complexes that then become trapped in capillary walls. (c) Tumor antigens can also become lodged in subepithelial locations where they can react with circulating antibodies. (d) Extrinsic processes, such as an infection with an oncogenic virus or altered immune function(9).

It is difficult to establish with certainty a causal relationship between a malignancy and glomerular changes, so causal relationships can only be estimated. In some patients, it is possible to detect tumor antigens within glomerular deposits, and a causal relationship is also suggested if proteinuria develops either six months before or after the malignancy diagnosis(6). Several reports have also documented sufficient resolutions of nephropathies after surgical excision of the tumors(10). In our patient, the diagnosis of glomerulonephritis was made approximately three months before the diagnosis of malignancy was established. The proteinuria resolved after chemotherapy, so we considered the relationship between the malignancy and the glomerulonephritis to be causal.

Although rare, other case reports of glomerulonephritis secondary to non-Hodgkin lymphoma have been reported. Rault et al. reported a 50-year-old patient with nephrotic syndrome who had a history of gastrointestinal bleeding, so an endoscopy was performed. The stomach appeared grossly abnormal, with giant gastric folds and multiple large and irregular gastric ulcers. A biopsy showed non-Hodgkin lymphoma, and treatment resulted in improvement of the renal disease(11).

Yeo et al. reported a case of a 58-year-old patient with non-Hodgkin MALT B-cell lymphoma, who presented with acute kidney injury, and nephrotic-range proteinuria. The patient's renal histopathology showed lupus-like proliferative nephritis. These authors suggested the glomerulonephritis was likely to be related to the malignancy because of the lack of clinical features of systemic lupus erythematosus and the low titers of anti-dsDNA antibodies. There was also an improvement in renal condition after one cycle of chemotherapy(12). Information concerning the long-term status of post-glomerulonephritis patients with non-Hodgkin lymphoma remission is still limited. Alshayeb et al. showed that 11 years after initial remission from non-Hodgkin lymphoma and glomerulonephritis, patients were still in clinical remission with normal kidney function and normal urinalysis(13).

Patients with glomerulopathy/nephropathy secondary to malignancy are managed according to the main cause. In the case of our patient, therapy for non-Hodgkin lymphoma. In general, management includes the following(6):

(i) Symptomatic treatment of the nephrotic syndrome/glomerulonephritis with appropriate diuretic therapy.

(ii) A detailed investigation of any abnormal electrolytes with appropriate therapy.

(iii) An evaluation of the level of malignancy to determine whether chemotherapy is appropriate and if the tumor can be removed.

(iv) A regular review all drug therapies to avoid the possibility of nephrotoxicity.

This patient was initially treated using a diuretic, an anti-lipid drug, and short-term dexamethasone for the superior vena cava syndrome. The patient was then given chemotherapy using cyclophosphamide, doxorubicin, vincristine, and prednisone. Their evaluation after the chemotherapy cycles showed both tumor remission and the disappearance of the proteinuria.

Conclusions

We have presented a case of secondary glomerulonephritis in a patient with non-Hodgkin lymphoma complicated by superior vena cava syndrome. For patients with glomerulonephritis, it is essential to explore the possibility of secondary glomerulonephritis. One of the possible etiologies of secondary glomerulonephritis that must be excluded is malignancy. The primary treatment for secondary glomerulonephritis due to malignancy is to treat the malignancy itself, either by surgery or by chemotherapy. Early and precise diagnosis with proper management can reduce both patient mortality and morbidity.

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