Case Report

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Lupus Nephritis Developed in Patient post-chemotherapy for Gestational Trophoblastic Neoplasia

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ABSTRACT

The association of GTN with kidney diseases is infrequent, with scarce published case reports. This case report describes the development of lupus nephritis in a 30-year-old female following chemotherapy for high-risk gestational trophoblastic neoplasia (GTN). Despite obtaining remission from GTN, the patient presented with persistent anemia, neutropenia, and renal dysfunction, directing to additional investigation. The diagnosis of lupus nephritis was confirmed through serological tests, renal biopsy, and the identification of specific autoimmune markers. This case promotes the importance of considering autoimmune diseases, comprising lupus nephritis, in the differential diagnosis of patients with hematologic anomalies after finishing her chemotherapy for GTN.

Keywords: Lupus Nephritis; Gestational Trophoblastic Neoplasia; Chemotherapy

Abbreviations: GTN: Gestational Trophoblastic Neoplasia; LN: Lupus Nephritis; SLE: Systemic Lupus Erythematosus; GFR: Glomerular Filtration Rate; WBC: White Blood Cell; TIBC: Total Iron Binding Capacity; PSTT: Placental Site Trophoblastic Tumor

Introduction

Gestational trophoblastic neoplasia (GTN) typically develops after a normal pregnancy or abortion and can be treated successfully with surgery and chemotherapy [1] The association of GTN with kidney diseases is infrequent; there are scarce published case reports [2-4]. Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE). We describe a case of LN that occurred in a young female in remission for nearly a year after the treatment of GTN; a kidney biopsy showed LN.

Case Presentation

A 30-year-old female with a medical history of preeclampsia and a first-trimester abortion presented with persistent anemia and neutropenia after completing chemotherapy for high-risk gestational trophoblastic neoplasia (GTN). She was diagnosed in August 2022 and underwent chemotherapy (Etoposide, Methotrexate, Dactinomycin, Cyclophosphamide, vincristine, cisplatin), completing the regimen on January 25, 2023, with serological remission achieved by January 11, 2023. However, she continued to experience low white blood cell counts and hypochromic microcytic anemia. By March 12, 2023, laboratory tests revealed mild renal injury with a glomerular filtration rate (GFR) of 46, and low iron levels and elevated ferritin, suggesting chronic inflammation. Despite these findings, the patient was clinically asymptomatic except for generalized joint pain. The patient had been initially treated with oral ferrous sulfate for anemia; however, persistent cytopenia prompted further investigation. Laboratory investigations showed a low white blood cell (WBC) count of 2.37, neutrophils of 0.74, hypochromic microcytic anemia with a hemoglobin of 9.5, and normal platelets at 236. Renal function tests showed mild renal impairment with a GFR of 46, while liver function tests remained normal. Hemolytic markers were negative, and hemoglobin electrophoresis was normal.

Iron studies indicated low serum iron (7.57), low transferrin (1.13), low total iron binding capacity (TIBC) of 28.3, and elevated ferritin (853), indicating chronic inflammation. Thyroid function tests were normal, and stool tests for occult blood and H. pylori were negative. A blood film showed normochromic, normocytic red blood cells with leukopenia but no evidence of hemolysis or abnormal cells. Autoimmune studies revealed strong positivity for SS-A/Ro antibodies, high anti-dsDNA antibodies (311.87), moderate positivity for Ro 52 antibodies, weak positivity for histone antibodies, and strong positivity for nucleosome antibodies, all strongly suggestive of SLE, particularly lupus nephritis. Complement levels were low, with C3 at 0.67 and C4 at 0.08, further supporting active autoimmune disease. Myeloma workup and viral serology for Hepatitis B, Hepatitis C, and HIV were negative. A renal biopsy was performed to investigate lupus nephritis, showing 14 glomeruli with mild mesangial matrix expansion and hypercellularity, consistent with an immune-mediated process. Tubular atrophy (15%) was noted, but no acute tubular injury was seen. The interstitial space showed 15% fibrosis with mild mononuclear infiltrates (Figure 1). Immunofluorescence showed granular mesangial staining for IgA, IgG, IgM, C3, C1q, kappa, and lambda, supporting lupus nephritis. Electron microscopy revealed variations in glomerular thickness and minor podocyte effacement, with no immune deposits. The renal biopsy findings were most consistent with minimal mesangial lupus nephritis (ISN/RPS Class I), suggesting early-stage renal involvement. Given the diagnosis of lupus nephritis, the patient was started on hydroxychloroquine to manage the autoimmune condition. She was also closely monitored for any progression of her renal function. The evolution was marked by a favorable outcome with the patient's normalization of neutrophil counts, improvement in renal function, and improvement of anemia following hydroxychloroquine treatment. Oral consent was taken from the patient for publication purposes.

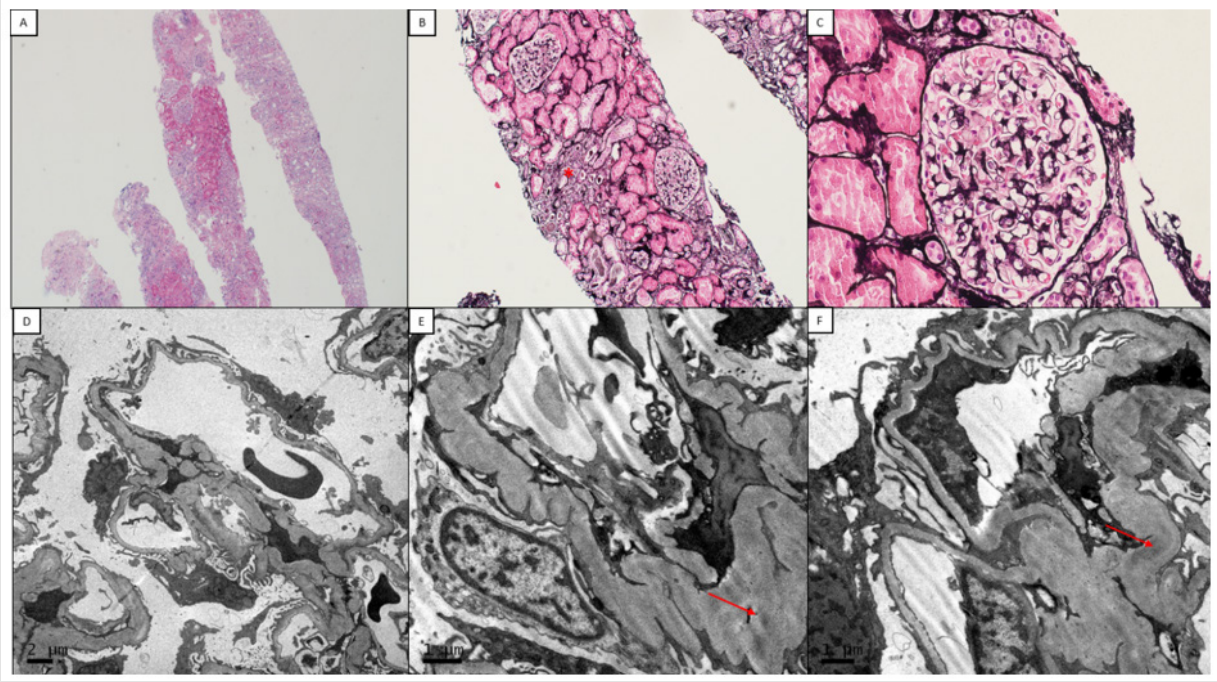

Figure 1:

- **A:** Low power image of the renal biopsy sample showing cortex with multiple glomeruli, H&E X 4.
- **B:** Two glomeruli with an adjacent area of interstitial fibrosis and tubular atrophy (asterisk), Jones X 20.
- **C:** Normal looking glomerulus with no mesangial or endocapillary proliferation and normal capillary walls, Jones X 40.
- **D:** Low magnification electron micrograph showing normal glomerular basement membranes and partial effacement of podocyte foot processes, X8000 magnification.
- **E and F:** Higher magnification electron micrographs showing small mesangial deposits (arrows). There were no deposits along the glomerular basement membranes, X12000 magnification.

Discussion

We describe a case of lupus nephritis in a 30-year-old female following chemotherapy for high-risk GTN. Despite achieving remission from GTN, the patient presented with persistent anemia, neutropenia, and renal dysfunction, leading to further investigation. The diagnosis of LN was confirmed through serological tests, renal biopsy, and identifying specific autoimmune markers. The association of renal lesions and GTN is infrequent. Only a few scarce reports have reported the association of kidney diseases with GTN [2-4]. When evaluating patients with hematologic and renal dysfunction abnormalities following GTN and no apparent cause, it's important to consider autoimmune diseases, including LN, in the differential diagnosis Xiao, et al. [5], described a case of a 31-year-old female with LN associated with a placental site trophoblastic tumor (PSTT). The patient presented with amenorrhea for 19 months and nephrotic syndrome, confirmed by kidney biopsy showing diffuse global proliferative LN. Despite glucocorticoid and cytotoxic therapy, her condition did not improve until a total abdominal hysterectomy was performed, resulting in the normalization of kidney function and β-hCG levels. The findings suggest that LN was secondary to PSTT, highlighting the rare association between renal lesions and gestational trophoblastic disease (GTN).

Impact of Pregnancy-Related Immune Modulations

The patient's history of preeclampsia and a first-trimester abortion can also influence the progression of autoimmune diseases. Women with preclinical autoimmune disorders who experience pregnancy complications like preeclampsia are at a higher risk of progressing to a definite autoimmune disease. Hormonal changes during pregnancy may exacerbate preclinical conditions, leading to their progression [6,7]. Pregnancy-related hormones significantly modulate immune responses, affecting both innate and adaptive immunity. These hormonal changes can alter cytokine production and immune cell function, impacting disease susceptibility and autoimmune conditions [8-10]. Autoimmune abnormalities are frequently observed in women with recurrent spontaneous abortions. Studies indicate that a substantial quota of women with unexplained recurrent abortions exhibit autoimmune serologic abnormalities, such as positive antinuclear antibodies and anticardiolipin antibodies [11-13].

Chemotherapy-Induced Immune Dysregulation

Chemotherapy agents, including etoposide, cisplatin, and methotrexate, while targeting cancer cells, can also disrupt immune tolerance and lead to autoimmune complications. Chemotherapy agents can cause severe immunological side effects, including the interruption of thymopoiesis and the depletion of tolerance-inducing thymic epithelial cells. This disruption can paradoxically lead to autoimmunity, as seen with drugs like cyclosporine A, cyclophosphamide, and dexamethasone, which affect thymic epithelial cells crucial for immune regulation [14]. Autoimmune complications are frequently observed in cancer patients undergoing chemotherapy. These include autoimmune cytopenia and other non-hematological autoimmune manifestations. The treatment of these complications often needs a focus on the autoimmune phenomena themselves, sometimes requiring the use of targeted therapies [15]. While chemotherapy is associated with autoimmune risks, immunotherapy, particularly immune checkpoint inhibitors, has been shown to have a higher incidence of autoimmune diseases. This includes conditions like hypothyroidism and colitis, which result from immune system hyperactivation [16-18].

Chemotherapy can cause significant damage to thymic epithelial cells, particularly the Aire+ medu lary TECs, which are crucial for inducing immune tolerance. This damage can lead to a temporary loss of tolerance and subsequent autoimmunity [14,19]. Chemotherapy-induced thymic involution results in a reduced output of naïve T cells and a restricted T cell receptor repertoire, impairing immune surveillance and leading to autoimmunity. The complex regeneration process can result in abnormal thymic hyperplasia, further complicating immune recovery [19]. There is gender-specific differences in thymic regeneration post-chemotherapy, with females showing different recovery kinetics, which may affect the risk of developing autoimmune diseases [20]. The fact that having upraised anti-ds DNA antibodies in our patient was reflective of an autoimmune process, which could have been activated or exacerbated by chemotherapy, making LN a credible diagnosis.

Conclusion

Autoimmune complications should be considered in the differential diagnosis of patients with GTN with persistent cytopenia and renal dysfunction. Early detection, vigilant monitoring, and appropriate management can significantly improve patient outcomes.

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