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Case Report

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Membranoproliferative Glomerulonephritis Associated with Type Ii Cryoglobulinemia, Revealing A Gastric Malt-Type Lymphoma (Morocco)

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1. Introduction

Cryoglobulinemic vasculitis (CV) is a rare systemic disease secondary to vascular deposits of cryoglobulin, an immunoglobulin capable of precipitating in the cold and resolubilizing upon warming. It primarily affects the skin, joints, peripheral nervous system, and kidneys. Renal involvement in CV clinically manifests as rapidly progressive glomerulonephritis or a nephritic syndrome and histologically as membranoproliferative glomerulonephritis (MPGN). CV is often associated with underlying conditions such as chronic infections (notably hepatitis C virus), autoimmune diseases, or certain cancers. Extra nodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) is a rare subtype of non-Hodgkin lymphoma (NHL) often linked to chronic inflammation. The stomach is the most common anatomical site associated with MALT lymphoma. While renal involvement in NHL is well documented, it is less common in MALT lymphoma. Here, we report an extremely rare case of MALT lymphoma with renal involvement, a rare cause of mixed CV associated with MPGN.

2. Observation

The patient, a 56-year-old woman, presented to the Nephrology department of Mohammed VI universal hospital center with gradual exacerbation of general edema and weight gain. Her medical history revealed a recurrent urticaria and purpura on both lower limbs for 6 years. Pangastritis for a year, and a prior diagnosis of vitamin B12 deficiency. A physical examination revealed a purpuric infiltrated ecchymotic lesions and urticarial papules lesions with pitting edema in the lower limbs (Figure 1).

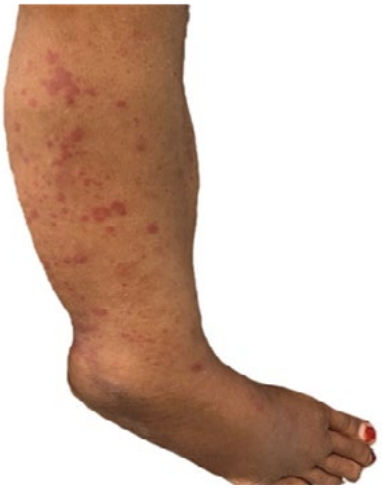

Figure 1

A complete blood count showed mild anemia: the hemoglobin level was 7,5g/dL, with a white blood cell count of 4,200/µL (with a lymphopenia of 770/µL) and a platelet count of 268 000/uL. Laboratory tests revealed proteinuria (urinary protein 0,97g/day) and hematuria [the urine sediment contained 33 red blood cells (RBCs) per high-power field]. The serum creatinine level was elevated (1, 7 mg/dl), with a low estimated glomerular filtration rate (40 mL/min/1.73 m2), low serum albumin level (24 g/L). Additionally, rheumatoid factor (RF) was detected, and cryoglobulinemia tested negative on two occasions. However, the consumption of complement C3 (0.6 g/L) and notably C4 (-0.006 g/L) prompted consideration of cryoglobulinemia. The patient was negative for anti-HCV antibodies and other autoantibodies (antinuclear antibodies, anti-cyclic citrullinated peptide antibodies, anti-Ro/SSA antibodies, myeloperoxidase-anti-neutrophil cytoplasmic antibodies, and serine proteinase3-anti-neutrophil cytoplasmic antibodies). Pathological findings from a skin biopsy revealed neutrophilic inflammation, with fibrinoid necrosis and fragmented neutrophilic nuclei, which are typical features of leukocytoclastic vasculitis. A percutaneous renal biopsy was performed and revealed glomerulonephritis with a membranoproliferative pattern of injury, and several glomeruli contained small cellular to fibrocellular crescents (Figure 2A). Hyaline pseudothrombi were not identified in the glomerular capillaries. A Congo red stain was negative for amyloid deposition. By direct immunofluorescence, there was granular mesangial and capillary wall staining for IgM (3+), IgG (1+) C3 (1+), and kappa and lambda light chain (3+) (Figure 2B).

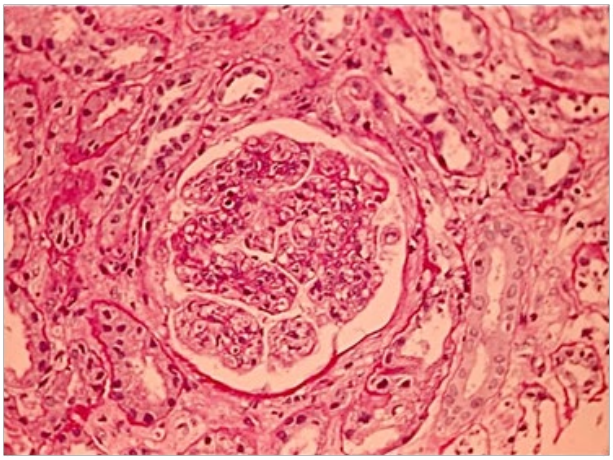

Figure 2A

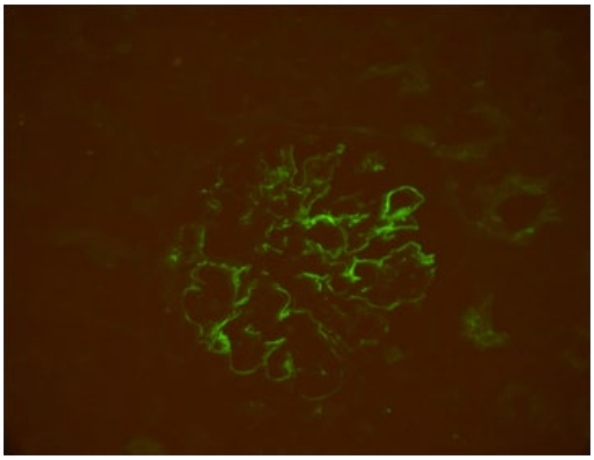

Figure 2B

Gastroscopy played a crucial role in diagnosing MALT-type gastric non-Hodgkin malignant lymphoma, unveiling an infiltrate of lymphoid cells expressing a monoclonal B-cell phenotype with CD20 and BCL-2. Bone marrow aspiration revealed no lymphoma infiltration, and computed tomography showed pulmonary nodules and abdominal lymphadenopathy, without hepatosplenomegaly. A final diagnosis of HP-negative MALT lymphoma and type II CV was made. The patient was transferred to our hematology department and is currently receiving chemoimmunotherapy RCHOP consisting of rituximab, cyclophosphamide, hydroxyadriamycin, oncovin and prednisone. The renal evolution was marked by the persistence of proteinuria (0,5g/24h) with serum creatinine at 1,5 mg/dl.

3. Discussion

We came across an exceptionally rare case featuring MALT lymphoma with renal involvement associated with type II cryoglobulinemia. While type I cryoglobulinemia is closely associated with underlying lymphoproliferative disorders, type II cryoglobulinemia is typically linked to HCV infection (observed in up to 90% of patients) [1,2]. Chronic B-cell stimulation appears to be the common pathogenic factor in type II cryoglobulinemias, promoting the synthesis of a monoclonal IgMκ with rheumatoid factor activity [3]. The most classical presentation corresponds to the Meltzer and Franklin triad, which includes asthenia, vascular purpura, and arthralgia. Renal involvement is reported in 10% of patients. Extrarenal signs usually precede glomerular involvement, sometimes by several years. It manifests through proteinuria, microscopic hematuria, or mild chronic renal insufficiency [4]. Typical laboratory findings in mixed cryoglobulinemia include an elevated RF, hypocomplementemia (C4 reduction out of proportion to C3) [5]. The elevated level of RF and presence of arthralgias in patients with cryoglobulinemic vasculitis can be misinterpreted as being indicative of RA. RF is one of the monoclonal components of mixed cryoglobulinemia, which is the reason why nearly all patients with cryoglobulinemic vasculitis have an elevated RF that improves with treatment.

From a histopathological perspective, it is a membranoproliferative glomerulonephritis with certain features, and in the typical form, the glomeruli show abundant endocapillary cellular infiltration, primarily macrophagic, associated with large intracapillary PAS-positive thrombi. The capillary walls are diffusely thickened with numerous double contour appearances. Vessels often show lesions of necrotizing vasculitis. These features, absent in idiopathic or lupus membranoproliferative glomerulonephritis, have led some authors to use the term "cryoglobulinemic glomerulonephritis." In immunofluorescence, the deposits are subendothelial and intracapillary, composed of immunoglobulins identical to those in the cryoprecipitate. In our observation, the absence of intracapillary

thrombi, the limited extent of double contour appearances, and the low abundance of deposits in immunofluorescence indicate that glomerular lesions in mixed cryoglobulinemias may be less typical (10 to 20% of cases). Glomerulonephritis can be segmental and focal with a more discreet macrophagic infiltrate and scanty subendothelial deposits, sometimes segmental, without intracapillary thrombi [3,4]. The standard of care for mixed cryoglobulinemic vasculitis is to remove the antigenic stimulus by treating the underlying disease, such as infection or malignancy. This emphasizes the significance of conducting a thorough etiological assessment, as evidenced in our case through a CT scan and gastroscopy. MALT lymphoma, a rare subtype of NHL, is thought to account for only 5-8% of all B cell lymphomas [6].

Chronic inflammation caused by HP, other microorganisms, and autoimmune diseases at extranodal sites can cause MALT lymphoma. The most common anatomical site of MALT lymphoma is the stomach, where it is associated with chronic gastritis induced by HP (up to 90% of cases). In our patient, no HP infection or apparent autoimmune disorders were documented. Recent studies have reported that non-HP Helicobacter infections can also cause gastric MALT lymphoma [7,8]. Treatment with high-dose glucocorticoids and rituximab is recommended for patients experiencing severe clinical manifestations. Rituximab is a murine monoclonal antibody designed to target the transmembrane protein CD20 present in developing and mature B-cells, initially intended for the treatment of NHLs. It is also considered a standard of care for both cryoglobulinemia and lymphoma [9,10]. Its effectiveness varies. It has shown moderate success in treating type II and type III cryoglobulinemia [10]. A retrospective chart review by Bryce et al. suggests that rituximab is most effective for cutaneous manifestations of type II cryoglobulinemia and minimally effective for renal disease [11]. However, the majority of case reports indicate an improvement in cryoglobulinemic nephropathy following rituximab treatment [12].

4. Conclusion

This case emphasizes the diagnostic significance of gastroscopy and the necessity for a thorough evaluation, particularly in cases involving cryoglobulinemia-associated conditions. The complexity of the presented case underscores the importance of an integrated and multidisciplinary approach in managing patients with rare and intricate manifestations of lymphoproliferative disorders.

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