A destructive nasal lesion and glomerulonephritis

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CASE PRESENTATION

A 19-year-old gravid Hispanic female (G_2P_1) at an unknown gestational age presented to the Emergency Room (ER) with new onset of gross hematuria and a 2-week history of swelling and tenderness of the nose and upper lip. She was prescribed a 10-day course of azithromycin for presumed cellulitis. After 10 days, she returned to the ER with worsening nasal swelling and complaints of lightheadedness. She denied fevers, chills, night sweats, hemoptysis, dysuria, shortness of breath, cough, oral ulcers, dysphagia, or rashes. The patient had moved to the US from Mexico 6 months prior to admission. Her only significant past medical history was chronic upper airway irritation for 2 years. There was no family history of renal disease.

Her temperature was 100.1°F, with a regular pulse of 110 beats/min, and respirations of 15/min. Blood pressure was 104/66 while seated. The nasal alae were edematous with erythema extending to the philtrum (Figure 1a). The nasal septum was necrotic with an anterior perforation and purulent discharge. The sclerae were anicteric and no oral erythema or ulceration was seen. There was no lymphadenopathy. Cardiovascular examination revealed a regular tachycardic rhythm with normal heart sounds and a grade III/VI systolic ejection murmur. Neurologic, pulmonary, and abdominal examinations were unremarkable. The extremities revealed normal pulses without edema or clubbing.

Laboratory values on presentation were as follows: hemoglobin, 6.1 g/dl (61 g/l) (normal range, 13–18 g/dl (130–180 g/l)); white-cell count, 5.5×10^9/l (normal range 4.3–10.8 $\times 10^9$/l) with a normal differential; platelet count, 348×10^9/l (normal range, 150–500 $\times 10^9$/l); BUN, 18 mg/dl (6.4 mmol/l) (normal range, 10–30 mg/dl (3.6–10.7 mmol/l)); serum creatinine, 1.7 mg/dl (150 μmol/l); serum protein, 5.8 g/dl (58 g/l) (normal range, 6.3–8.2 g/dl (63–82 g/l)); serum albumin, 2.7 mg/dl (normal range, 3.5–4.9 g/dl (35–49 g/l)). The creatinine clearance was 28 ml/min. Serum sodium, potassium, chloride, calcium, bicarbonate, glucose, transaminases, and alkaline phosphatase were normal. Urinalysis showed 3+ protein and 4+ blood. Microscopic examination of the urine showed many RBCs per high power field (too numerous to count), multiple red blood cell casts, waxy casts, epithelial casts, and hyaline casts. The 24-h urine protein was 3984 mg. The following serologies were negative or normal: anti-neutrophil cytoplasmic antibody, anti-nuclear antibody, anti-double stranded DNA antibody, hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus antibody, anti-glomerular basement membrane antibody, antistreptolysin-O, and serum complements. The erythrocyte sedimentation rate was greater than 140 mm/h.

Computer tomography of the sinuses disclosed extensive bilateral nasal soft tissue swelling extending to the medial premaxillary region associated with a small perforation of the nasal septum and local hemorrhage. Chest radiograph was unremarkable. The ultrasound of the abdomen was consistent with a pregnancy of 9 weeks and 5 days. Renal ultrasound showed normal-sized kidneys with normal echogenicity.

The patient was hospitalized for blood transfusions and supportive care. She was treated empirically with nafcillin for nasal cellulitis. A renal biopsy and endoscopic nasal biopsy were performed. Although anti-neutrophil cytoplasmic antibody serologies were negative, the possibility of Wegener's granulomatosis was strongly entertained based on the presentation with a destructive nasal lesion, hematuria, and acute renal failure.

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NASAL BIOPSY FINDINGS

The endoscopic nasal biopsy showed a dense infiltrate composed of irregular medium-sized to large atypical lymphoid cells exhibiting a high mitotic index admixed with smaller lymphocytes (Figure 1b). Focally, there were areas of necrosis and vascular invasion. By immunohistochemistry, the majority of the atypical lymphoid cells were CD2+, CD3+ (cytoplasmic), CD5−, CD7−, and both CD4− and CD8−. The atypical cells also expressed CD56 (neural cell adhesion molecule), a marker of natural killer (NK) cells). Scattered mature CD4+ or CD8+ lymphocytes were also present. CD20 showed few B cells and CD21 revealed no evidence of follicle formation. *In situ* hybridization performed on paraffin-embedded tissue sections revealed positive staining of most cells with an oligonucleotide probe specific for Epstein–Barr virus encoded RNA. The morphological features in combination with immunophenotype were consistent with extranodal NK/T-cell lymphoma, nasal type (previously referred to as 'lethal midline granuloma').

KIDNEY BIOPSY FINDINGS

The kidney biopsy contained 13 glomeruli for light microscopy, none of which were globally sclerotic. Glomeruli displayed moderate diffuse and global increase in mesangial cell number and matrix associated with mesangial expansion by glassy eosinophilic, fuchsinophilic deposits (Figure 1c). Superimposed on these mesangial proliferative features, 10 glomeruli displayed segmental endocapillary proliferation with focal infiltrating mononuclear leukocytes and rare duplication of glomerular basement membrane. In three of these glomeruli, the endocapillary proliferative lesions exhibited necrotizing features. Ten (77%) glomeruli contained segmental to circumferential crescents that ranged in age from cellular to fibrocellular (Figure 1c). There was mild

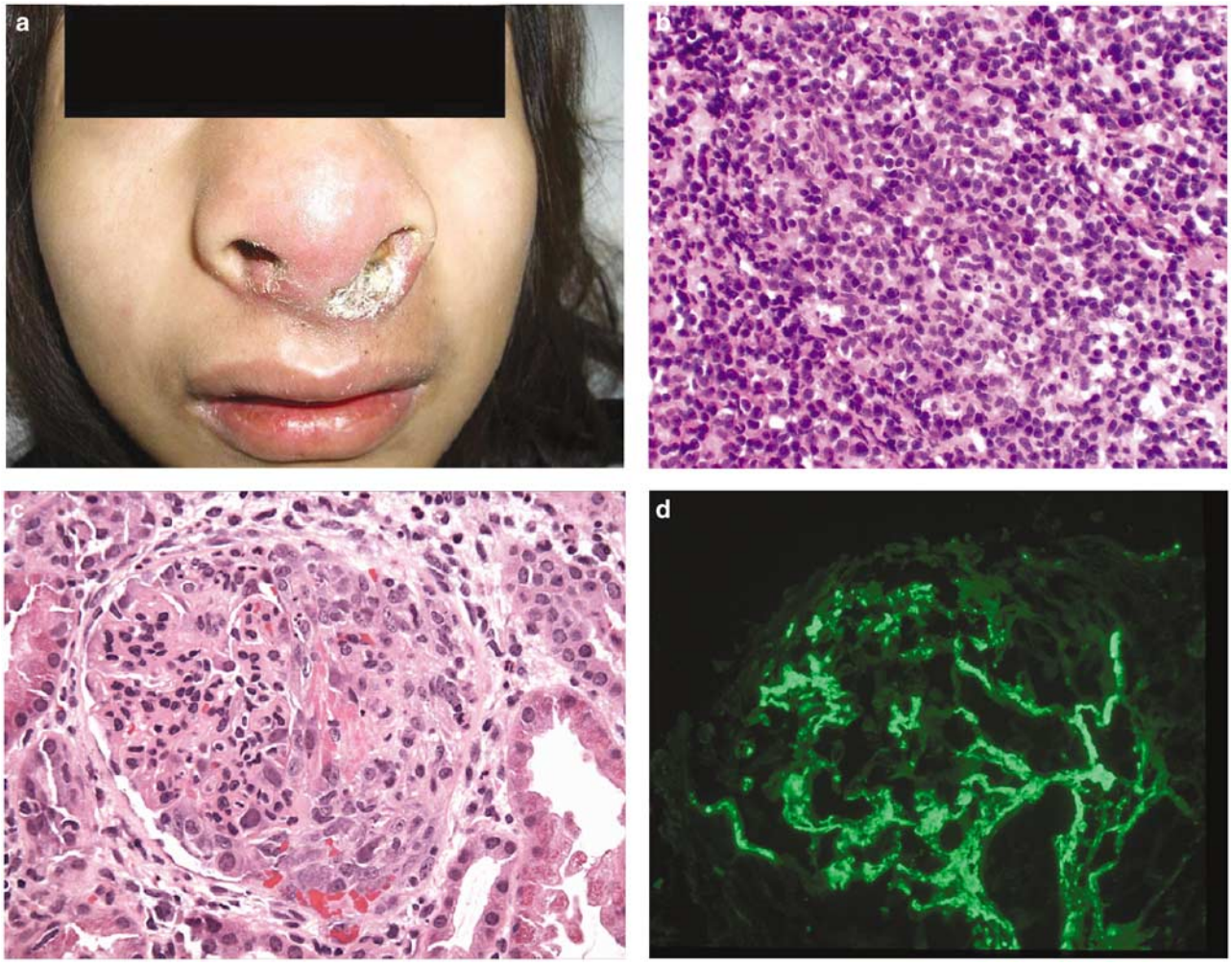

Figure 1 | Pathologic findings. (**a**) There is swelling and erythema of the nose extending to the upper lip. The external nasal septum appears ulcerated with purulent exudate. (**b**) The nasal biopsy (performed on the left nares) reveals an atypical dense infiltrate of medium-sized lymphoid cells admixed with a few smaller cells (H&E, original magnification ×400). (**c**) A representative glomerulus shows compression of the tuft by a large cellular crescent admixed with fibrin. In the distorted tuft, there is global mesangial and segmental endocapillary hypercellularity. (H&E, original magnification ×400). (**d**) Immunofluorescence staining shows intense positivity for IgA in a global mesangial distribution (original magnification ×400).

focal tubular atrophy and interstitial fibrosis involving approximately 10% of the cortex. Approximately 80% of the cortex had interstitial expansion by edema and moderate diffuse polymorphic inflammatory infiltrates of small mature lymphocytes, monocytes, scattered plasma cells, and neutrophils. There were abundant red blood cell casts associated with tubular degenerative and regenerative changes. Arteries and arterioles were unremarkable. No arteritis was identified. *In situ* hybridization performed on a paraffin-embedded renal biopsy section with an oligonucleotide probe specific for Epstein–Barr virus-encoded RNA was negative.

Three glomeruli were studied by immunofluorescence and showed 2–3+ granular global mesangial and segmental glomerular capillary wall staining for IgA (Figure 1d) and C3, with trace IgG, 1+ IgM, negative C1q, 1+ kappa, and 2–3+ lambda.

By electron microscopy, the mesangial areas were globally expanded by moderate increase in mesangial cell number and matrix containing numerous small to medium-sized mesangial electron dense deposits. There was segmental endocapillary proliferation associated with segmental subendothelial extension of small electron dense deposits. No endothelial tubuloreticular inclusions were seen. The glomerular tufts were focally compressed by cellular crescents. There was moderate effacement of foot processes involving approximately 60% of the glomerular capillary surface area. No tubulointerstitial electron dense deposits were identified.

FINAL DIAGNOSIS

Diffuse endocapillary and extracapillary proliferative glomerulonephritis, severe, consistent with IgA nephropathy (associated with NK/T-cell lymphoma, nasal type).

CLINICAL FOLLOW-UP

Following the results of nasal and renal biopsy, the patient underwent elective termination of pregnancy and was started on high-dose chemotherapy with cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) every 3 weeks. The patient's creatinine returned to her presumed baseline of 0.7 mg/dl (62 μmol/l), however the hematuria and proteinuria persisted. At 3 months after starting chemotherapy, she developed sepsis and died; no autopsy was performed.

DISCUSSION

IgA nephropathy (IgAN) is the most common cause of glomerulonephritis worldwide. Patients typically present either with periodic macrohematuria (40–50%) or persistent microhematuria (30–40%), associated with proteinuria and, in many cases, renal insufficiency.[1–2] There is often a history of antecedent respiratory tract infection. Although most cases of IgAN are idiopathic, identification of secondary IgAN (such as because of cirrhosis, inflammatory bowel disease, or malignancy) serves more than an academic purpose, as treatment strategies and prognosis differ depending on the underlying cause.

Pathomechanisms implicated in primary and secondary IgAN can be classified into three non-mutually exclusive categories: defects in IgA clearance, overproduction of IgA, and derangements in mucosal immunity. IgA exists in two subclasses: IgA1, produced by plasma cells in the GI tract, respiratory tract, bone marrow, lymph nodes, and spleen; and IgA2, produced by plasma cells only in the GI and respiratory tracts. Evidence suggests that the IgA deposits in the glomeruli of patients with IgAN are exclusively polymeric IgA1.[3] Studies have shown that abnormal galactosylation of IgA1 predisposes to mesangial deposition,[4] and this undergalactosylation may be due to a decrease in leukocyte β-1,3-galactosyltransferase activity.[5] The undergalactyosylated hinge region of IgA1 may generate antigenic determinants that are recognized by naturally occurring IgG and IgA antibodies, leading to the production of circulating immune complexes containing IgG and IgA1.[6]

Defective clearance is thought to be the dominant cause of IgAN in hepatic disease, and up to one-third of cirrhotics will have glomerular deposition of IgA, with or without clinical evidence of renal disease.[7] The hepatic asialoglycoprotein receptor is the principal site of IgA catabolism, suggesting that loss of this receptor through hepatocyte depletion may be directly responsible for the decreased clearance.[8] In addition, it has been postulated that the hepatic asialoglycoprotein receptor may not clear undergalactosylated IgA1 as effectively as intact IgA1.[9]

Much like decreased clearance, overproduction of IgA can promote IgAN. Up to 50% of patients with IgAN have elevated serum IgA levels.[2] Of note, overproduction of IgA is common in human immunodeficiency virus infection and 8% of human immunodeficiency virus infected individuals will have mesangial deposition of IgA on autopsy.[10,11] Overproduction of IgA may not be sufficient to cause IgAN, however, as exemplified by the rarity of IgA nephropathy secondary to IgA-producing multiple myeloma. In one case report of IgAN in the setting of IgA-producing multiple myeloma, the IgA isolated was abnormally glycosylated, again underscoring the importance of this biochemical modification in the pathogenesis of IgAN.[12]

Alterations in mucosal immunity that promote increased synthesis of IgA have often been implicated in the development of IgAN. This mechanism is supported by the frequent temporal association of antecedent respiratory and GI tract infections with episodes of hematuria in IgAN or its systemic variant, Henoch–Schonlein purpura. Secondary IgAN is seen in patients with celiac disease, ulcerative colitis, Crohn's disease, and cystic fibrosis, among other chronic diseases affecting the gastrointestinal and respiratory mucosa.[1]

IgAN has rarely been associated with lymphoma. Only eight cases have been reported in the English literature, including three with Hodgkin's disease, one with mucosa-associated lymphoid tissue (MALT) lymphoma (a low grade B-cell non-Hodgkin's lymphoma), and four with mycosis fungoides (a cutaneous form of non-Hodgkin's T-cell lymphoma) (Table 1).[13–19] The eight cases included six males

Table 1 | Main features of nine reported cases of IgAN associated with lymphoma

Case	Age/sex	Type of lymphoma	Clinical renal manifestations	Glomerular pattern	Therapy	Length of follow-up	Renal outcome	Reference
1	70/male	CTCL	Hematuria, renal failure	Mesangial proliferative GN	NP	NP	NP	Ramirez *et al.*[13]
2	56/male	CTCL	Hematuria, renal failure	Mesangial proliferative GN	NP	NP	NP	Ramirez *et al.*[13]
3	66/female	CTCL	Hematuria, proteinuria	Diffuse mesangial and focal enodocapillary proliferative and crescentic GN	NP	NP	Persistent hematuria (died of lymphoma complications)	Moe *et al.*[14]
4	62/male	MALT lymphoma	Gross hematuria, proteinuria, renal failure	Diffuse mesangial proliferative and crescentic GN	Chlorambucil	>1 year	CR (normal urinalysis and renal function)	Mak *et al.*[15]
5	29/male	Hodgkin's disease	Hematuria, proteinuria	Focal proliferative and crescentic GN	Combination chemotherapy, radiotherapy	2 years	CR	Blanco *et al.*[16]
6	44/male	Hodgkin's disease	Nephrotic syndrome, hypertension, renal failure, hematuria	Diffuse crescentic GN	Combination chemotherapy, steroids	6 months	CR	Cherubini *et al.*[17]
7	60/female	Hodgkin's disease	Hematuria, proteinuria, renal failure	Diffuse mesangial proliferative and focal crescentic GN	Combination chemotherapy, steroids	>1 year	CR (normal urinalysis and renal function)	Bergmann *et al.*[18]
8	54/male	CTCL	Hematuria, proteinuria, renal failure	Focal mesangial proliferative and crescentic GN	PUVA, etretinate, topical steroids	NP	NP	Sato *et al.*[19]
9	19/female	Extranodal NK/T-cell lymphoma, nasal type	Gross hematuria, proteinuria, renal failure	Diffuse proliferative and crescentic GN	Combination chemotherapy	3 months	Persistent hematuria and proteinuria, normal serum creatinine (died of sepsis)	Current report

CR, complete recovery; CTCL, cutaneous T-cell lymphoma; GN, glomerulonephritis; MALT, mucosa-associated lymphoid tissue; NP, data not provided; PUVA, psoralen plus ultraviolet A irradiation.

and two females, with a mean age of 55 years (range, 29–70). All eight patients presented with hematuria, including gross hematuria in one. Proteinuria was documented in six patients and full nephrotic syndrome in one. Six patients had renal failure. On light microscopic examination of the renal biopsy, mesangial hypercellularity was present in seven cases, focal endocapillary hypercellularity in two, and crescent formation in six (diffuse in two and focal in four). Renal infiltration by lymphoma was found on biopsy only in the case of mucosa-associated lymphoid tissue lymphoma, together with tonsillar and gastrointestinal involvement.[15] Importantly, complete renal recovery was achieved in four of the five patients with available follow-up following treatment with chemotherapy, with or without radiotherapy or steroid treatment, including all three cases associated with Hodgkin's disease and the one case associated with mucosa-associated lymphoid tissue lymphoma.[15–18] In one case associated with mycosis fungoides, hematuria persisted and the patient subsequently died of lymphomatous visceral involvement and infectious complications.[14]

This is the first report of IgAN occurring in association with extranodal NK/T-cell lymphoma, nasal type. NK/T-cell lymphoma, nasal type, is a unique type of non-Hodgkin's lymphoma highly associated with Epstein–Barr virus infection.[20] Archaic synonyms include angiocentric lymphoma and lethal midline granuloma. It is rare in Western populations and much more common in Asia and Central and South America.[21–22] Clinical features include obstructive and destructive lesions primarily of the nasal region and sinuses, although other extranodal sites have been reported. Histologically, the lymphomatous infiltrate often displays a diffuse pattern, but angiocentricity with vascular invasion and necrosis are common. The infiltrate is usually composed of medium-sized to large cells with the following characteristic immunophenotype: CD2+, CD56+, surface CD3−, cytoplasmic CD3+, Epstein–Barr virus +, and T-cell receptor.[20] Most cases are of NK-cell origin, although rare cases derive from T cells, hence the designation extranodal NK/T (instead of NK)-cell lymphoma, nasal type. The prognosis of extranodal NK/T-cell lymphoma, nasal type is poor. The median survival was 11 months with combined chemotherapy and radiotherapy in a large retrospective study from Hong Kong.[23] A higher disease stage with multiorgan involvement (such as nodal, cutaneous, pulmonary, and hepatosplenic) and B symptoms (fever, sweats, or weight loss) are associated with decreased survival.[21]

The pathogenesis of IgAN associated with lymphoma is unclear. A study of 254 patients with cutaneous T-cell lymphoma demonstrated that 24.8% had elevated IgA levels, suggesting a role for overproduction of IgA.[24] In addition, cutaneous T-cell lymphoma , by compromising the integument, may cause derangements in local immunity.

In our case, the close temporal relationship between the development of NK/T-cell lymphoma, nasal type and the clinical onset of IgA nephropathy, as well as the improvement in renal function following chemotherapy, support that the two conditions are pathogenetically related. Nasal mucosal necrosis and ulceration because of lymphoma may have stimulated hyperactivity of the local mucosal immune system. The spectrum of lymphoma associated with IgA nephropathy should be expanded to include NK/T-cell lymphoma, nasal type.

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