An Unusual Case of Alcoholic Liver Disease Associated with Secondary IgA Vasculitic Nephritis presenting as Rapidly Progressive Glomerulonephritis

Articoli originali

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ABSTRACT

IgA nephropathy (IgAN) is a fairly common association with alcoholic liver disease. However, IgA vasculitis (IgAV) is quite an uncommon association with alcoholic liver cirrhosis and only a handful of cases have been reported in literature. Secondary IgAN usually presents in a docile manner, progressing slowly in about 5-25 years. It is usually responsive to steroid therapy, very rarely progressing to End-Stage Renal Disease.

Here, we present a man in his late 50s, a known hypertensive and alcohol related liver-cirrhotic, who presented to our hospital with rash and rapidly progressive renal failure (RPRF). He was diagnosed with IgA nephritis with IgA vasculitis (IgAVN). His diagnosis was confirmed with skin and renal biopsy.

He was started on renal replacement therapy for his renal failure and began oral steroid therapy. After administration of steroid therapy for 6 months, the patient recovered and was dialysis independent with stable renal parameters.

KEYWORDS: IgA nephropathy, Alcoholic Liver disease, rapidly progressive glomerulonephritis, IgA vasculitis

Background

Secondary IgA nephropathy is a well-known complication of alcohol related chronic liver disease [1], however, IgA vasculitis with nephropathy secondary to liver disease is quite rare and only a handful of cases have been reported in literature.

The presentation of IgA nephropathy secondary to liver cirrhosis varies from clinically silent disease to nephrotic or nephritic syndromes [2]. Very rarely, it can present as end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). The natural progression involves development of end stage renal disease within 20 years of presentation [3]. The incidence of rapidly progressive renal failure in IgA nephropathy in less than 10%.

However, the clinical profiling of patients with IgA nephritis in IgA vasculitis secondary to alcoholic liver disease, is lacking in literature.

Here we present a case of secondary IgA vasculitis with nephritis (IgAVN) in a patient with decompensated alcoholic liver disease, presenting with rapidly progressive glomerulonephritis (RPGN).

Case Report

A man in his late 50s presented to our hospital with complaints of bilateral pedal oedema and shortness of breath for a month. He had a history of rash, predominantly over bilateral lower limbs, beginning five days before presentation to our hospital, which progressed to involve his upper limbs and back during hospital stay. He also reported a history of abdominal pain and haematochezia one week prior to admission. However, at presentation, his bowel pattern was normal, and no further episodes of haematochezia were noted during the hospital stay.

He had no history of fever, sore throat, visible haematuria, decreased urine output, hematemesis, abdominal pain or distention. He had no history of such episodes in the past or during childhood. He had no history of analgesic overuse or drug abuse.

His comorbidities included systemic hypertension, coronary artery disease, heart failure with mid-range ejection fraction of 45%, and alcohol use disorder. Baseline creatinine done during a hospital admission to treat alcohol dependence 6 months ago, was 1.0 mg/dl, with a bland urinary examination. He neither had a history suggestive of inflammatory bowel disease nor skin disease in the past.

Physical examination revealed bilateral pitting pedal oedema and healing faint hyperpigmented rash over his lower extremities (Figure 1a-1b), however, upper limbs and back revealed fresh non-blanching purpuric rash during hospital stay (Figure1c-1d).

Abdominal examination showed mild distension and ascites; however, it did not reveal palpable organomegaly. Per rectal examination revealed grade II haemorrhoids. Respiratory system examination revealed bilateral normal vesicular breath sounds, cardiovascular examination was normal and neurological examination showed no focal neurological deficits.

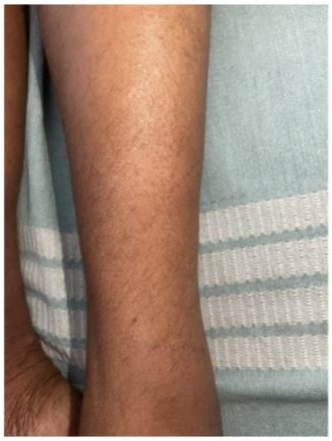
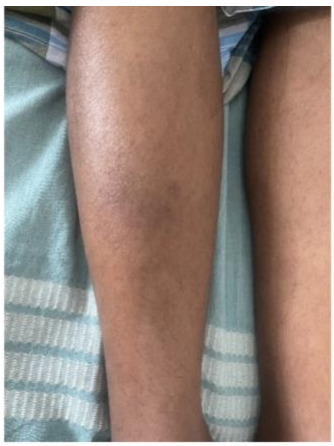

Figure 1a-1b. Faint hyperpigmented macular lesions on bilateral lower limbs.

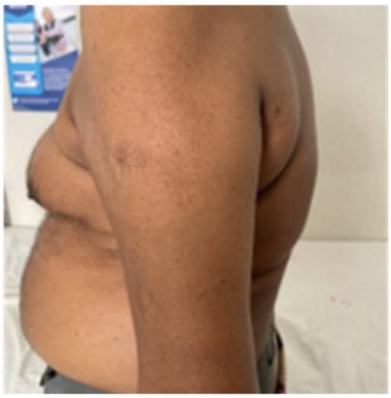
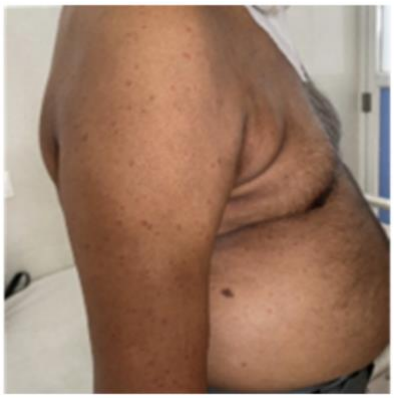

Figure 1c-1d. Purpuric rash on bilateral upper limbs.

Investigations

The patient was evaluated and found to have deranged renal parameters, severe metabolic acidosis, hyperkalaemia, anaemia, microscopic haematuria, albuminuria and hypoalbuminemia (Table 1). Serum complement levels were normal. Testing for HIV, HbSAg and HCV was negative by CLIA method.

Upon observation for 24 hours, his urine output was less than 0.5ml/kg/hr. In view of rapidly progressive renal failure, acidosis and hyperkalaemia, he was initiated on renal replacement therapy in the form of haemodialysis. Ultrasound examination revealed kidneys of size 9.3×3.9 cm (right) and 8.8×4.1 cm (left), coarse echotexture of the liver with nodules of varying sizes and moderate ascites. Upper gastrointestinal endoscopy showed small oesophageal varices with portal hypertensive gastropathy. Dermatologist was consulted for the rash and a suspicion of vasculitis was opined. Since the patient presented to us on day 5 after the onset of the skin lesions, the biopsy of the lesions histopathologically revealed nonspecific inflammatory findings. However, he developed new onset skin lesions during hospital stay. He was subjected to a repeat skin biopsy within 24 hours, which showed features of leucoclastic vasculitis. Investigations were done for vasculitic work up, which revealed negative study for serum cANCA and pANCA.

In view of RPGN and for specific diagnosis, he was subjected to a renal biopsy. The light microscopy of the biopsy revealed 11 glomeruli, out of which 4 were globally sclerotic. All viable glomeruli showed mesangial hypercellularity with double contour sign, three glomeruli showed segmental endocapillary hypercellularity and fibrocellular crescent in one glomerulus and 35% of the core showed interstitial fibrosis and tubular atrophy (Figure 2a). PAS staining of renal section showed mesangial hypercellularity with double contour sign and segmental endocapillary hypercellularity

(Figure 2b). Masson's trichome staining of renal section showed fibrocellular crescent in one glomeruli (Figure 2c). Immunofluorescence showed IgA 3+ and C3 2+ positivity in the mesangium and capillary loops (Figure 2d).

Hence, a diagnosis of IgA nephritis with IgA/HSP vasculitis (based on EULAR/PRINTO/PRESS CRITERIA) was made [4, 5].

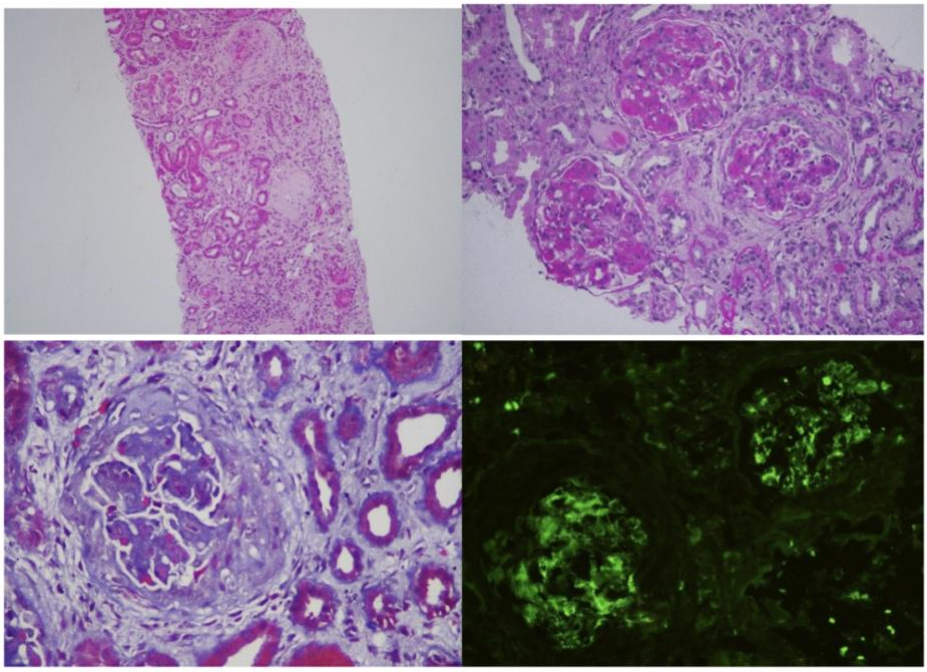

Figure 2. a) Hematoxylin and eosin staining of renal biopsy; b) PAS staining of renal section showing mesangial hypercellularity with double contour sign and segmental endocapillary hypercellularity; c) Masson's trichome staining of renal section; d) Immuno-Florescence staining of renal section-showing positive IgA staining in the mesangium and capillary loop.

Differential diagnosis

Since the renal biopsy revealed definitive IgA mesangial deposits, a diagnosis of IgA nephropathy was made. Given the underlying alcoholic liver disease, the possibility of secondary IgA nephropathy was considered. With the history of palpable purpuric rash, leucoclastic vasculitis on skin biopsy and biopsy proven glomerulonephritidis with IgA deposition, a diagnosis of co-existing systemic IgA vasculitis was made (based on EULAR/PRINTO/PRESS Criteria of HSP) [4, 5].

Treatment

The patient was initiated on renal replacement therapy, in view of his severe metabolic acidosis, hyperkalaemia, volume overload state and oliguria.

Supportive therapy in the form of fluid restriction, salt restriction and lifestyle modification were advised. However, given persistent hyperkalaemia, RAASi (Renin angiotensinogen aldosterone system inhibition) therapy could not be attempted. Because of his crescentic glomerulonephritis and rapidly progressive renal failure, corticosteroid therapy was contemplated. Due to his pre-existing gastropathy, oral deflazacort was chosen as the preferred oral steroid and he was started on a dose of 0.5 mg/kg/day. He continued receiving other supportive medications. Patient was followed-up for a period of 6 months on steroid therapy.

The frequency of RRT was gradually reduced, and he eventually became dialysis-independent with stabilized renal parameters.

Outcome and follow-up

The patient was followed-up for a period of 7 months. He continued receiving steroid therapy, which was tapered to the minimum effective dosage. In view of his recurring skin rashes, he was started on immunomodulators Mycoph enolate Mofetil therapy on his 10-week follow-up at a dose of 500 mg twice a day. It was started on this therapy in consultation with the rheumatologist and dermatologist in view of recurring skin lesions.

He continued receiving dialysis support for 2 months post-diagnosis, was eventually weaned off dialysis support and was dialysis independent with stabilised renal parameters. His latest creatinine was stable at 3.2 mg/dl and latest urine PCR was 1.7 mg/mmol. He was ambulant, able to carry out normal daily activities.

Baseline		Follow-up	
Investigation	Result	Investigation	Result
Haemoglobin	9.8g/dl	Creatinine	3.2 mg/dl
PCV	50 50	Urea	61 mg/dl
RBC	3.2	Sodium	136 mmol/L
WBC	7760/cumm	Potassium	4.1 mmol/L
Neutorophils	62.9%	Chlroide	100 mmol/L
Lymphocytes	15.3%	Bicarbonate	21 mmol/L
Monocytes	13.4%	U.PCR	1.7mg/mmol
Eosiniphils	4.9%		
Basophils	0.5%		
Platelets	150,000/ml		
ESR	54		
Sodium	132 mmol/L		
Potassium	6.5 mmol/L		
Chlroide	100 mmol/L		
Bicarbonate	18 mmol/L		
Calcium	8.2 mg/dl		
Phosphorous	6.1 mg/dl		
Magnesium	2 mg/dl		
Creatinine	4.2 mg/dl		
Urea	51 mg/dl		
BUN	24		
ALT (SGOT)	24IU/ml		
AST (SGPT)	29IU/ml		
Albumin	2.8 g/dl		
Urine Routine			
Protein (albumin)	+++		
Sugar	Nil		
RBC	20-22per HPF		
WBC	0-1per HPF		
Cast / Crystals	not found		
Bile salt	Nil		
Urine protein	175		
Total volume urine	400ml		
24hrs urine protein	700		
Anti HIV	Negative		
Anti HBsAg	Negative		
Anti HCV	Negative		

Table 1. Blood investigations.

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Discussion

Alcoholic liver disease is one of the most common causes of secondary IgA nephropathy [2]. However, IgA vasculitis with renal involvement is quite uncommon association with alcoholic liver diseases, with only a handful of cases having been described in literature till date [6, 8]. IgA vasculitis is commonly found in paediatric population, rarely in the adult population [9]. The incidence of IgA vasculitis with nephritis (IgAVN) in adults, is reportedly 1.3 cases/100,000 adults per year [10]. The renal involvement in adults with IgAVN is much more severe than paediatric population, often progressing in 50% of the cases [10]. In a case report published in 2020, a review of IgAV secondary to liver disease was made and only 4 out of 13 cases were secondary to alcohol related cirrhosis [8], out of which one case report documented necessity for renal replacement therapy [11].

IgA vasculitis, previously termed Henoch Schonlien purpura, involves IgA deposition in the vessel walls and organs of non-lymphoid origin. Various theories have been postulated regarding the etio-pathogenesis of primary and secondary IgA vasculitis/nephropathy. Over the past years, there have been several reviews outlining similarities between IgA vasculitis and IgA nephritis. Most recently the four hit hypothesis model has been described in the pathogenesis of IgAVN in paediatric population by Hastings et al. This includes the following postulates: “1) elevated production of IgA1 glycoforms with some O-glycans deficient in galactose in the hinge region (galactose-deficient IgA1; Gd-IgA1); 2) generation of circulating IgG autoantibodies specific for Gd-IgA1; 3) formation of pathogenic circulating Gd-IgA1-containing immune complexes, which can activate the alternative complement pathway; 4) kidney deposition of the Gd-IgA1-IgG immune complexes from the circulation and induction of glomerular injury” [14].

Defective clearance of IgA circulating immune complexes, galactose deficiency and increased CD89 expression on mononuclear cells due to liver cirrhosis can predispose to systemic manifestations of IgAVN [6]. In addition, there is a disruption of the intestinal tight mucosal barrier and bacterial translocation secondary to alcohol intake, which increases the serum IgA levels. The circulating IgA1 can also directly activate neutrophils via the IgA Fc receptor Fc alphaRI (CD89) leading to neutrophil migration and a cascade of inflammatory response. IgAN is a consequence of increased IgA deposits secondary to either primary or secondary causes, with liver cirrhosis being one of them.

There often occurs a diagnostic dilemma in recognizing cases of IgA vasculitis in the adult population. Due to difficulty in diagnosing IgA vasculitis with the previous ACR criteria in 2010, EULAR/PRINTO/PRES (The European League Against Rheumatism, Paediatric Rheumatology International Trials Organization and Paediatric Rheumatology European Society) brought in a new consensus in the diagnosis of IgA vasculitis [4]. Initially formulated for paediatric population, the above-mentioned criteria was found to have a good sensitivity and specificity in diagnosing IgAV in adult population as well [5]. In our case the diagnosis was made clinically and histopathologically based on renal biopsy. The presentation of rash in IgA vasculitis is variable, predominantly affecting the lower limbs. However, a positive biopsy finding in the skin lesion is highly dependent on the timing of the punch biopsy sample. Lesions biopsied 48 hours after the onset, can show non-specific features of inflammation and repair, rather than active leucocytoclastic vasculitis [12], and cannot be relied upon, as was the case in our patient initially. Repeat biopsy done on fresh lesions which the patient developed during hospital stay revealed features suggestive of leucoclastic vasculitis. The clinical profile of IgAVN secondary to alcohol related liver disease is lacking in literature. Case reports have previously been reported with rapidly progressive renal failure in IgAN secondary to liver disease [13]. However, IgAVN secondary to alcoholic liver disease presenting with rapidly progressive renal failure is quite rare. Renal replacement therapy could be a necessary modality of treatment in acute IgAVN. Following this, immunotherapy should be considered at the earliest.

Take-Home Messages

- Incidence of new-onset rash in patients with underlying liver cirrhosis should prompt investigation with basic renal function testing and urine analysis.
- Modified EULAR/PRINTO/PRESS criteria cater better to the adult population for diagnosis of IgA vasculitis.
- The presentation of IgA vasculitis can vary from clinically silent disease to rapidly progressive renal failure.
- Biopsy of vasculitic skin lesion is time specific and should be performed within 24-48 hours to obtain conclusive results.

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BIBLIOGRAPHY

1. Tota M, Baron V, Musial K, Derrough B, Konieczny A, Krajewska M, et al. Secondary IgA Nephropathy and IgA-Associated Nephropathy: A Systematic Review of Case Reports. J Clin Med. 2023 Jan;12(7):2726. https://doi.org/10.3390/jcm12072726
2. Pouria S, Feehally J. Glomerular IgA deposition in liver disease. Nephrol Dial Transplant. 1999 Oct 1;14(10):2279–82. https://doi.org/10.1093/ndt/14.10.2279
3. Kwon CS, Daniele P, Forsythe A, Ngai C. A Systematic Literature Review of the Epidemiology, Health-Related Quality of Life Impact, and Economic Burden of Immunoglobulin A Nephropathy. J Health Econ Outcomes Res. 2021 Sep 1;8(2):36–45. https://doi.org/10.36469/001c.26129
4. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch–Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010 May 1;69(5):798–806. https://doi.org/10.1136/ard.2009.116624.
5. Hočevar A, Rotar Z, Jurčić V, Pižem J, Čučnik S, Vizjak A, et al. IgA vasculitis in adults: the performance of the EULAR/PRINTO/PRES classification criteria in adults. Arthritis Res Ther. 2016 Mar 2;18(1):58.
6. Elhani I, Pillebout E, Terrier B, Hankard A, Vrtovsnik F, Jourde-Chiche N, et al. IgA Vasculitis With Underlying Liver Cirrhosis: A French Nationwide Case Series of 20 Patients. J Rheumatol. 2021 May 1;48(5):735–40. https://doi.org/10.3899/jrheum.200293
7. Gupta N, Kim J, Njei B. Spontaneous Bacterial Peritonitis and Henoch-Schönlein Purpura in a Patient with Liver Cirrhosis. Case Rep Med [[Internet]]. 2015 [[cited 2023 May 17]];2015. Available from: https://doi.org/10.1155/2015/340894.
8. Kanthi Bommareddy, Rabah Alreshq, David Jones, Gurpreet Singh. A Very Rare Case of Immunoglobulin A Vasculitis in an Adult with Alcoholic Liver Cirrhosis.
9. Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B. IgA vasculitis (Henoch–Shönlein purpura) in adults: Diagnostic and therapeutic aspects. Autoimmun Rev. 2015 Jul 1;14(7):579–85. https://doi.org/10.1016/j.autrev.2015.02.003
10. Licia Peruzzi, Rosanna Coppo. IgA vasculitis nephritis in children and adults: one or different entities? [[Internet]]. Pediatric Nephrology; 2020. https://doi.org/10.1007/s00467-020-04818-7
11. Jong Hwan Jung. Henoch–Schönlein purpura nephritis and colitis in an adult patient with alcoholic liver cirrhosis. Kidney Res and Clin Prac. https://doi.org/10.1016/j.krcp.2016.04.003.
12. Carlson JA. The histological assessment of cutaneous vasculitis. Histopathology. 2010;56(1):3–23. https://doi.org/10.1111/j.1365-2559.2009.03443.x
13. Kaneko T, Arima R, Arakawa Y, Aoki M, Fukuda K, Fukui M, et al. [[Two cases of rapidly progressive nephritic syndrome complicated with alcoholic liver cirrhosis]]. Nihon Jinzo Gakkai Shi. 2011;53(1):60–7.
14. Hastings MC, Rizk DV, Kiryluk K, Nelson R, Zahr RS, Novak J, et al. IgA vasculitis with nephritis: update of pathogenesis with clinical implications. Pediatr Nephrol Berl Ger. 2022 Apr;37(4):719–33. https://doi.org/10.1007/s00467-021-04950-y