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RESEARCH LETTER

Origin of poorly galactosylated IgA1 other than mucosa: a viewpoint from a report on patient with IgA vasculitis

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ABSTRACT

Patients presenting monoclonal gammopathy of renal significance (MGRS) and IgA vasculitis collectively have rarely been reported. This study reports one patient with monoclonal IgA and λ, and with IgA positive-mesangial proliferative glomerulonephritis. The patient manifested slight chronic nephritic syndrome, and his serums tested positive for M protein (monoclonal IgA and λ). As a result of bone wear, the plasma cell ratio of these patients was confirmed to be mildly increased in peripheral blood smears. Just like typical IgA nephropathy or IgA vasculitis patients, serum poorly galactosylated IgA1 antibodies were found in the patient compared to the controls. The patient was diagnosed with mild mesangial proliferative IgA vasculitis based on renal biopsy. Besides, immunofluorescence/immunohistochemistry confirmed immune deposits predominantly containing galactose-deficient IgA1 (GD-IgA1) and λ in the glomerular mesangium and the walls of the skin's blood vessels. The pathological findings support the hypothesis that monoclonal IgA, which originate from bone marrow plasma cells, rather than mucosally primed B cells, also may be galactose deficient. This may be a new pathological source of IgA-proliferative glomerulonephritis.

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Introduction

IgA nephropathy (IgAN) or IgA vasculitis are the most common glomerular diseases worldwide, especially in Asian regions. It is the main cause of ESRD in primary kidney disease. Renal biopsy is the gold standard for the diagnosis of IgAN. Since the first description of the IgAN in 1968 by Jean Berger, several investigations on accumulated physiological mechanism of this glomerulonephritis (GN) have been carried out in recent decades [1,2]. The multi-hit hypothesis including galactose-deficient IgA1 (GD-IgA1) production (Hit1), IgG, or IgA autoantibodies that recognize GD-IgA1 (Hit2), immune complex formations (Hit3), and IgA deposition on glomerulus (Hit4) have been recognized. Hit 1, poorly galactosylated IgA1 [3] antibodies were found to be present in serum and glomerular filtrate of patients with IgAN for more than 20 years. Earlier studies have confirmed that the production of poorly galactosylated IgA1 was the main triggering factor for IgAN or IgA vasculitis. Yet, the factors controlling IgA1 *O*-glycosylation are still unclear. Smith AC et al. reported that as compared to IgA1 synthesized from systemically primed B cells, IgA1 synthesized from mucosally primed B cells is relatively poorly galactosylated [4]. The cases described below may originate a controversy on the source of poorly galactosylated IgA1.

Case presentation

A 47-year-old man presented with recent onset proteinuria and hematuria with normal kidney function. Physical examination revealed scattered, asymmetrical purpura on both the

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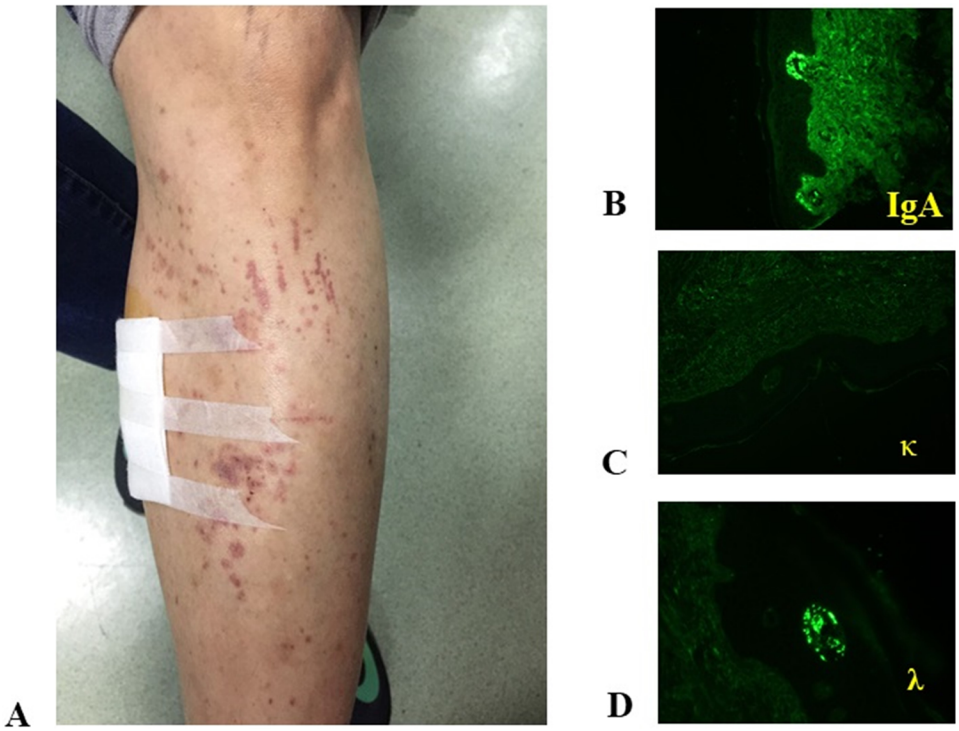

Figure 1. (A) Low limb purpura of patient. (B, C, and D) Skin biopsy confirmed that IgA and light chain lambda deposition were positive around the blood vessels of purpura, but the light chain kappa deposition was negative.

lower limbs (as shown in Figure 1A), and he sensed mild joint pain on palpation.

Blood tests revealed normal liver functions, positive serum HBsAg, HBcAb, and HBeAb. But HBV-DNA quantification was normal (1.17×10^2 IU/mL). M-band (2.4%) was detected in serum protein electrophoresis. Serum immunofixation electrophoresis showed positive monoclonal IgA λ (Figure 2). Although both free κ and λ light chains increased, the ratio of free κ/λ (1.0461) was found to be normal. The cryoglobulin test was negative. Furthermore, the blood levels of GD-IgA1 were tested using the lectin-based method as previously described [5,6] to obtain a value of 352.3 U/mL (mean value of GD-IgA1 for healthy control was 288 U/mL, the mean value of Gd-IgA1 for IgAN patients was 316 U/mL). Routine urine examination revealed mild hematuria (300–500 mg/d) and proteinuria. Erythrocyte phase-detection indicated more than 85% malformed urinary red blood cells.

Kidney biopsy demonstrated mild mesangial proliferative glomerulonephritis with monoclonal IgA deposits. Immunofluorescent staining indicated significant IgA and C3 deposits on the mesangium and segmental capillary walls. Only λ chain deposits were observed, while κ chain deposits were negative (Figure 3). Immunohistochemistry staining showed the absence of HBsAg and HBcAg deposits. Congo red staining was also negative. PAS and PASM staining have been depicted in Figure 4. Mild mesangial cell proliferation was observed under electron microscopy, with slight electron-dense deposits in mesangial areas (Figure 5).

In order to find out whether the monoclonal IgA deposition induces mesangial proliferation, the GD-IgA1 staining was performed on frozen tissue. Surprisingly, immunofluorescence

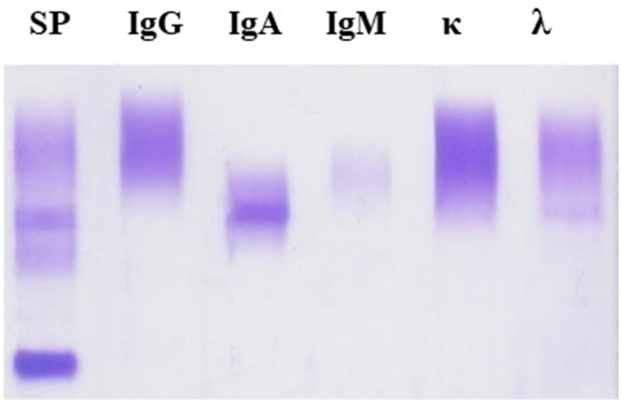

Figure 2. Result of serum immunofixation electrophoresis of patient.

indicated GD-IgA1 (KM55 antibody) deposits on the mesangium (Figure 6).

A skin biopsy was accomplished to know about the rashes. Immunofluorescent staining indicated significant IgA and λ chain deposits on the vascular wall (Figure 1B–D).

Bone marrow aspiration and biopsy were performed twice. The results exhibited the plasma cell ratio was 1%–3%. Polynuclear plasma cells were seen. Bone marrow biopsy showed normal myeloproliferation. Plasma-like cells were evident in small amounts. Immunohistochemistry indicated clonal hyperplasia (CD38+, Kappa-, Lambda+, and CD235a+). Bone marrow flow cytometry detection showed that 0.12% of abnormal nucleated plasma cells, which strongly expressed CD138 and CD38, cLambda and CD22, and partly expressed CD28, CD81, and CD27, without CD19, CD56, CD117, CD13,

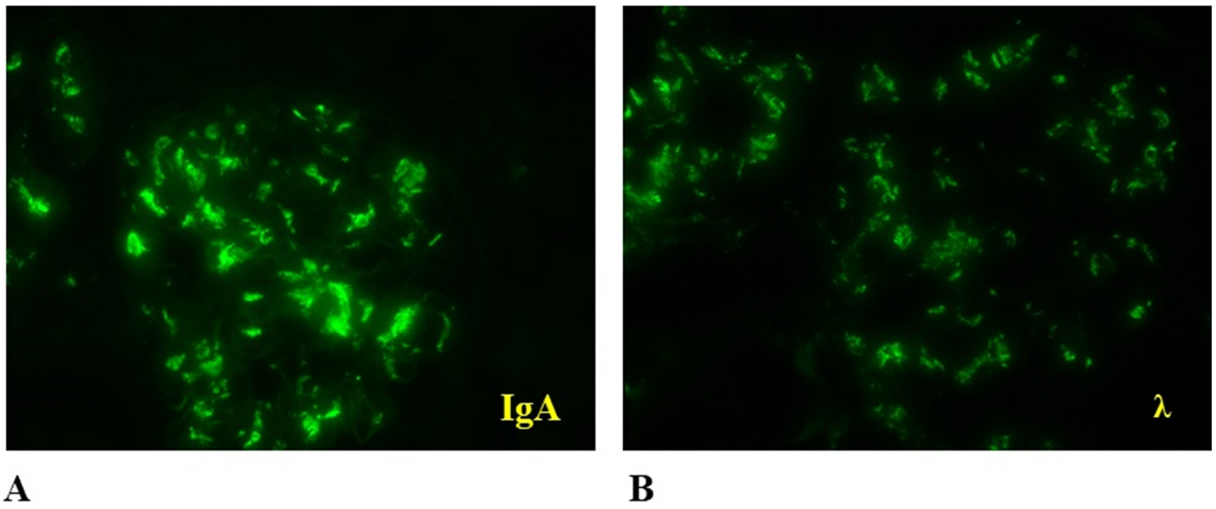

Figure 3. (A) Immunofluorescence staining of biopsied renal tissue of patient showing that IgA deposition was strongly positive. (B) Immunofluorescence staining showing that light chain lambda deposition was also positive, but the light chain kappa was negative.

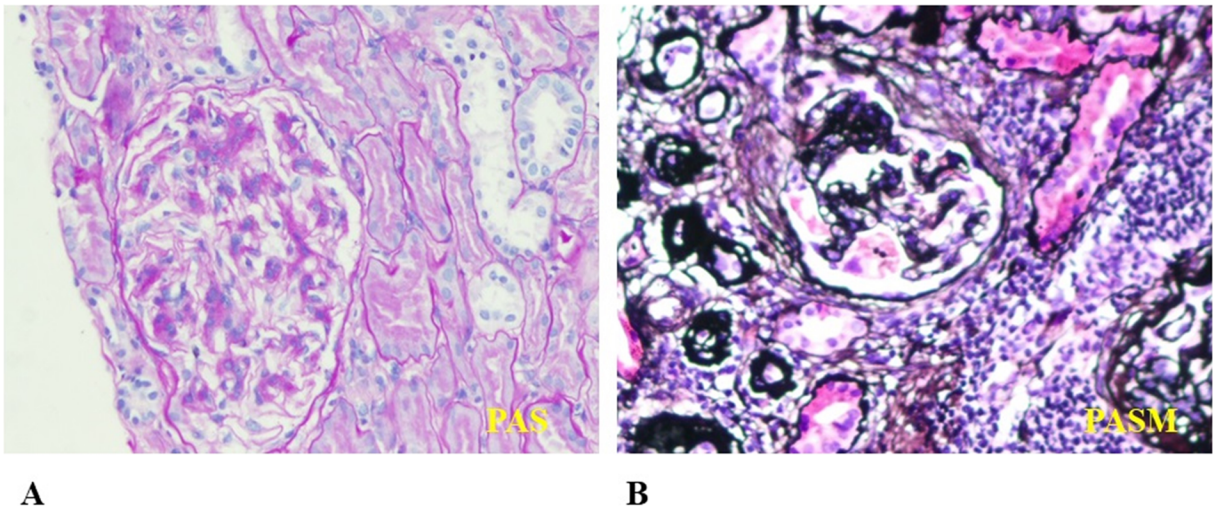

Figure 4. Patient (A and B): PAS and PASM staining showed glomerulus presented mild mesangial proliferation.

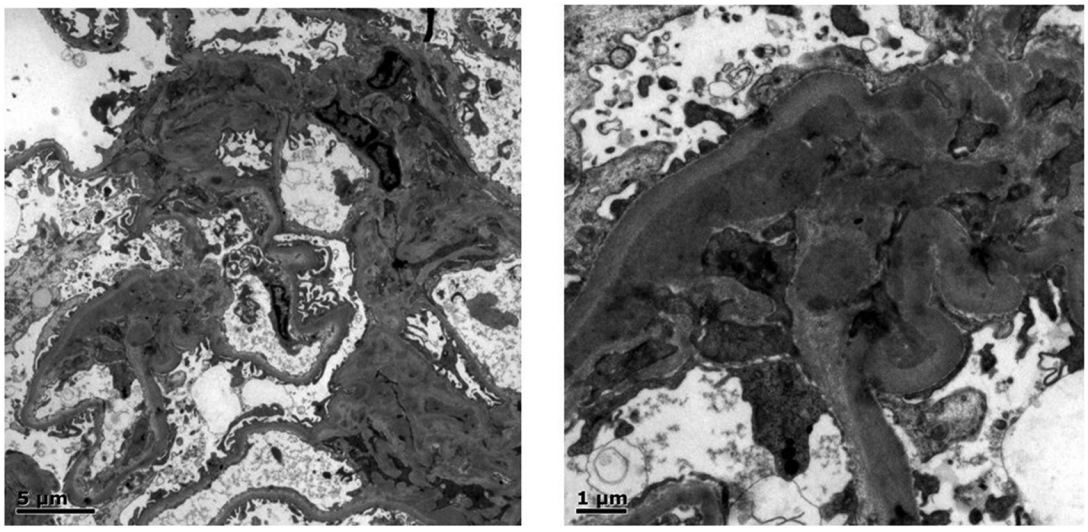

Figure 5. Patient (A and B): Typical transmission electron micrographs. Mild mesangial cell proliferation was observed under electron microscopy with slight electron-dense regions in mesangial areas.

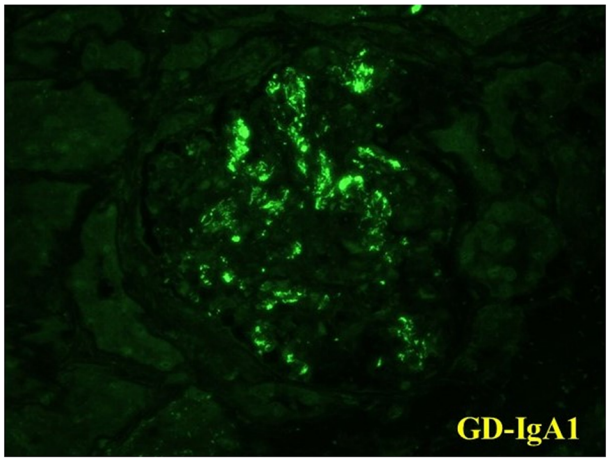

Figure 6. For patient, GD-IgA1 deposition was positive in the mesangial area.

CD33, CD20, and cKappa expression. Bone marrow FISH test demonstrated normal results.

Throughout nearly two years of observation and follow-up, serum creatinine level in the patients is stable. 24 h urine showed nearly 300–500 mg protein levels with malformed red blood cells.

Discussion

When pathologists initially diagnosed the kidney pathology of this patient, they first noticed the obvious restrictive expression of his light chain lambda. Although the light chain staining of many IgAN patients has more light chain λ than light chain k, it is not common to have completely restrictive expression like this patient. Studies on multiple myeloma of IgA type have been reported [7]. Unlike the above case, in IgA type multiple myeloma, most monoclonal IgA-λ deposition in renal tissue may follow passive deposition, without pathological pro-proliferation function. However, the above-mentioned case prompted that monoclonal IgA may be functional, acted like in polyclonal poorly galactosylated IgA1 in IgAN. Poor serum GD-IgA1 and positive GD-IgA1 staining in the mesangial area supports this deliberation. This phenomenon urges for the review of pathogenic IgA.

Elevated serum monoclonal IgA may be detected in IgA myeloma; however, decreased sialylation or galactosylation of hinge-region *O*-glycans of IgA1 was rarely reported in the past [8]. In the above-described case, the patients were diagnosed with MGRS, instead of IgA myeloma. However, in this case, GD-IgA1 with lambda was detected in the mesangial area. As compared to the controls, the patient presented a lower number of *O*-glycan chains per hinge region of the glycopeptide. Similar to IgA nephropathy or purpuric nephritis, complement C3 was positive in the mesangial area. The phenomenon suggests that, like regular IgA nephropathy, complement activation is also involved in this pathological process.

In healthy individuals, IgA is known to be induced in mucosal B cells in the first step. IgA^+ plasmablast (PB) recirculates and is homing to the intestinal mucosa. Terminal B-cells then differentiate into plasma cells with local IgA production. IgA exports through the intestinal epithelial cell layer at last [9]. B-cell homing to mucosal and peripheral tissues is mediated by specific combinations of chemokine receptors and adhesion molecules. Homing to the bone marrow is mediated *via* the chemokine ligand-receptor 4 (CKCR4), which is expressed on all types of PBs, as well as combinations of chemokine receptors 10 (CCR10). Although most of the polyclonal IgA1 in serum is considered to originate from bone marrow, the part of IgA1 is not yet proven to be pathogenic.

In IgAN and IgA-vasculitis patients, the pathogenic factor for IgA nephropathy was confirmed to be the defective IgA1. Poorly galactosylated IgA1 was found in serum and glomerular filtrate of IgAN patients in 2001 [3]. The key observation helped establish the cause and pathological consequence of alterations in the complement of serum IgA1 *O*-glycoforms in IgAN. In IgAN patients, IgA1 *O*-glycosylation may be differentially regulated in IgA1-secreting plasma cells [10]. The site of IgA1 production was partially related to the local cytokine milieu. Previous studies have confirmed that the majority of poorly galactosylated IgA1 was synthesized from mucosally primed B cells, rather than systemically primed B cells [11]. However, based on the results of the case reports presented herein, it can be speculated that GD-IgA1 may be produced from bone marrow plasma cells, rather than the mucosally primed B cell, which may be another source of IgA vasculitis.

Conclusion

Conventional theory confirmed the mucosal origin of Gd-IgA1 as the culprit in IgA nephropathy. Nonetheless, this case reports one patient with monoclonal IgA induced IgA vasculitis. Before the four hits hypothesis, the cause and mechanism of GD-IgA1 production was an enigma. We at this moment believe that plasma cells of bone marrow can also produce monoclonal GD-IgA1, which induces IgA vasculitis.

Disclosure statement

I declared that the results presented in this paper have not been published previously in whole or part. No potential conflict of interest was reported by the authors.

Informed consent

Written informed consent was obtained from the patient for publication of this case (including publication of images).

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Data availability statement

All data are included in the manuscript.

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