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Severe Hyperferritinemia with Preserved Transferrin Saturation in Genetically Confirmed X-Linked Alport Syndrome: A Case Report

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Case Report

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Abstract

Background

Alport syndrome is an X-linked inherited kidney disease caused by mutations in type IV collagen genes (COL4A3, COL4A4, and COL4A5) that affect the glomerular basement membrane and can lead to sensorineural hearing loss and eye abnormalities. This disease, which can cause hematuria, proteinuria, and in more severe cases chronic kidney disease, is characterized by bilateral and high-frequency sensorineural hearing loss, eye dysfunction, and in rare cases, aortic aneurysm; however, abnormalities in iron metabolism are not commonly described.

Case Presentation:

We report a case of persistent and marked hyperferritinemia in a patient with genetically confirmed Alport syndrome, without blood transfusion, significant inflammation, or hereditary hemochromatosis. In 2016, a patient whose etiology of proteinuria and hematuria was investigated showed no abnormalities in iron parameters in laboratory tests performed at that time, while as of 2021, serum ferritin levels were found to be > 1000 µg/L. Abdominal ultrasound and MRI scans revealed severe hepatosplenomegaly. Minimal increases in infection and inflammation markers did not explain this severely elevated ferritin level. Hemochromatosis gene mutations were tested in several different laboratories, and no mutations were detected.

Conclusion

This case suggests a possible dysregulation of iron metabolism in a patient diagnosed with Alport syndrome, beyond the inflammation associated with conventional chronic kidney disease. The interaction between collagen IV mutations and systemic inflammation and iron regulatory pathways may require more detailed investigation.

Introduction

Alport syndrome results from mutations in type IV collagen genes (COL4A3, COL4A4, and COL4A5), leading to structural abnormalities of the glomerular basement membrane and progressive chronic kidney disease (1). It causes hematuria and progressive proteinuria in the kidneys and is characterized by extrarenal manifestations, including sensorineural hearing loss.

Ferritin is an acute phase reactant that increases in response to oxidative stress and cytokine release (2). In severe hyperferritinemia (> 1000 ng/mL), exclusion of hereditary hemochromatosis, transfusion-induced iron overload, malignancies, liver diseases, or macrophage activation syndromes is necessary (3).

The relationship between collagen IV mutations and systemic iron metabolism is not yet fully defined. Here, we report a genetically confirmed case of X-linked Alport syndrome presenting with persistent hyperferritinemia exceeding 2000 ng/mL despite preserved transferrin saturation and negative HFE mutation analysis, suggesting a potential secondary iron redistribution phenotype.

Case Presentation

A 38-year-old female patient presented to the hospital in 2016 with a spontaneous miscarriage at the seventh week of her first pregnancy. Complete urinalysis at that time revealed 1 + proteinuria. Quantitative evaluation showed a 24-hour urinary protein excretion of 1540 mg/day. Serum creatinine and estimated glomerular filtration rate (eGFR) were within normal limits. Renal ultrasonography measured the dimensions of the right kidney at 150 x 35 mm and the left kidney at 91 x 32 mm, with preserved parenchymal thickness (12 mm on both sides). Kidney contours and localization were normal, and no pelvicalyceal enlargement was observed. Initial immunological evaluation showed ANA 1+, ANCA negative, normal immunoglobulin A, G, and M levels, normal complement C3, and decreased C4 (15 mg/dL). Suspicion of lupus nephritis arose due to persistent proteinuria and isolated complement deficiency. Kidney biopsy revealed findings suggestive of focal segmental glomerulosclerosis without chronic tubulointerstitial damage or global glomerulosclerosis. Renal function was preserved throughout the follow-up period.

A dynamic upper abdominal MRI performed in August 2021 showed hepatomegaly (long axis of the right lobe 206 mm) and splenomegaly (long axis of the spleen 132 mm). Decreased T1 and T2 signal intensities were observed in both the liver and spleen, raising suspicion of iron accumulation or hematological pathology.

An abdominal scan performed in October 2025 revealed hepatomegaly with a craniocaudal liver diameter of 185 mm and splenomegaly with a spleen long axis of 130 mm. Liver parenchymal density was decreased in both T1 and T2 weighted sequences, without focal solid or cystic lesions. On November 27, 2025, a custom liver and heart iron quantification MRI (T2*) showed a significant decrease in liver T2* values (1.5–1.8 ms), consistent with severe hepatic iron accumulation. Cardiac T2* values were measured as 30–35 ms in the interventricular septum and free wall, remaining within normal limits and ruling out myocardial iron accumulation.

Serial ferritin levels, which had been increasing since 2019, were above 2000 ng/mL in 2021 (Fig. 1). Despite severe hyperferritinemia, transferrin saturation remained within the normal range. Inflammatory markers (CRP, ESR) and transaminases were normal.

HFE mutation analysis performed in 2021 and 2025 was negative. Due to persistently high ferritin levels and radiological evidence of severe hepatic iron deposition, weekly therapeutic phlebotomy was initiated, and deferasirox treatment was administered when ferritin levels remained significantly elevated. In 2025, a diagnosis of progressive bilateral sensorineural hearing loss, confirmed by audiometry, was made. Given the combination of renal involvement and hearing loss, genetic testing was performed, and a

pathogenic COL4A5 mutation consistent with X-linked Alport syndrome was identified. Initially, low-dose angiotensin-converting enzyme inhibitor therapy was initiated due to persistent proteinuria; however, treatment was discontinued due to hyperkalemia and hypotension. To reduce the progression of renal disease, SGLT2 inhibitor therapy, which has been shown to be effective in previous studies, was initiated. The patient, who visited the outpatient clinic for kidney function tests during the second week of SGLT2 inhibitor treatment, showed no increase in creatinine levels, and proteinuria measured in spot urine had decreased to 700 mg/day.

Discussion

Type IV collagen mutations lead to structural disruption of the glomerular basement membrane, causing progressive renal damage and sterile inflammation in the kidney (4). In Alport-associated nephropathy, activated macrophages exhibit a pro-inflammatory phenotype, leading to cytokine release. IL-6 increases hepcidin synthesis, and hepcidin degrades ferroportin, reducing iron release into circulation (5).

Persistent macrophage activation and hepcidin-mediated iron retention may therefore lead to hyperferritinemia (6). Chronic kidney injury can further contribute to this process (7). Another potential contributing mechanism may be alterations in erythropoiesis associated with inflammation, leading to functional iron deficiency and increased intracellular iron retention despite preserved transferrin saturation (8).

The relationship between collagen IV mutations and systemic iron metabolism is not yet fully defined, and excessive and persistent hyperferritinemia in Alport syndrome has not been described in the literature. It is unclear whether this results from inflammatory disease activity, hepcidin-induced iron retention, or a previously unknown immunometabolic phenotype within Alport syndrome.

Recognizing this pattern is clinically important because in nephrology practice, severe hyperferritinemia is often interpreted as primary iron overload. In patients with hereditary nephropathy, misclassification can lead to unnecessary investigations or inappropriate long-term treatment strategies. This case highlights the importance of integrating transferrin saturation, genetic assessment, and quantitative MRI findings when interpreting significantly elevated ferritin levels.

Key laboratory and imaging findings are summarized in Table 1.

Table 1
Key Laboratory and Imaging Findings

Parameter	Finding
Peak ferritin	> 2000 ng/mL (persistent)
Transferrin saturation	21–32% (normal range)
Hemoglobin	Normocytic, stable
HFE mutation	Negative
Liver T2* MRI	Severe hepatic iron deposition (1.5–1.8 ms)
Cardiac T2* MRI	Normal
Audiometry	Bilateral sensorineural hearing loss
Genetic testing	Pathogenic COL4A5 mutation

Further prospective studies are needed to clarify whether this represents a reproducible immunometabolic phenotype within collagen IV–associated nephropathy.

Conclusion

This case describes persistent hyperferritinemia with radiologically confirmed severe hepatic iron accumulation in a patient with genetically confirmed X-linked Alport syndrome, without transfusion exposure or hereditary hemochromatosis.

The co-occurrence of renal involvement, bilateral and progressive sensorineural hearing loss, hepatosplenomegaly, and severe hyperferritinemia suggests that chronic basement membrane damage may affect systemic iron metabolism in addition to structural glomerular pathology.

These findings are consistent with a macrophage-mediated secondary iron redistribution process, representing an immunometabolic dimension in Alport syndrome. Clarifying this situation is also clinically important because in such patients, severe hyperferritinemia can be misinterpreted as primary iron overload, ultimately leading to unnecessary or incorrect interventions.

Further studies are needed to clarify whether dysregulated iron metabolism in collagen IV-related nephropathies reflects inflammatory disease activity, reticuloendothelial iron retention, or a contributing pathogenic mechanism. Increased awareness of this potential relationship could improve the diagnostic evaluation of unexplained hyperferritinemia in hereditary glomerular disorders.

The main educational implications of this case are summarized in Table 2.

Table 2
Teaching Points

Teaching Points
Severe hyperferritinemia with normal transferrin saturation should prompt evaluation for secondary iron redistribution mechanisms.
In hereditary nephropathies, chronic sterile inflammation may contribute to altered iron metabolism.
Hepatic T2* MRI is useful for distinguishing patterns of iron deposition.
Negative HFE mutation analysis does not exclude non-classical iron accumulation patterns.
Alport syndrome may rarely present with systemic iron dysregulation.

Abbreviations

MRI
Magnetic Resonance Imaging
HFE
Hereditary Haemochromatosis Protein
ANA
Anti Nuclear Antibody
ANCA
Anti Neutrophil Cytoplasmic Antibody
CRP
C-Reactive Protein
ESR
Erythrocyte Sedimentation Rate
SGLT2 inhibitors
Sodium-Glucose Co-transporter 2 inhibitors

Declarations

Ethics approval and consent to participate

Ethical approval was not required for this case report according to institutional policy. Written informed consent was obtained from the patient for participation in this study.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The author declares that she has no competing interests.

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Authors' contributions

TU conceptualized the study, collected the clinical data, analysed the findings, and wrote the manuscript. The author read and approved the final manuscript.

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Figures

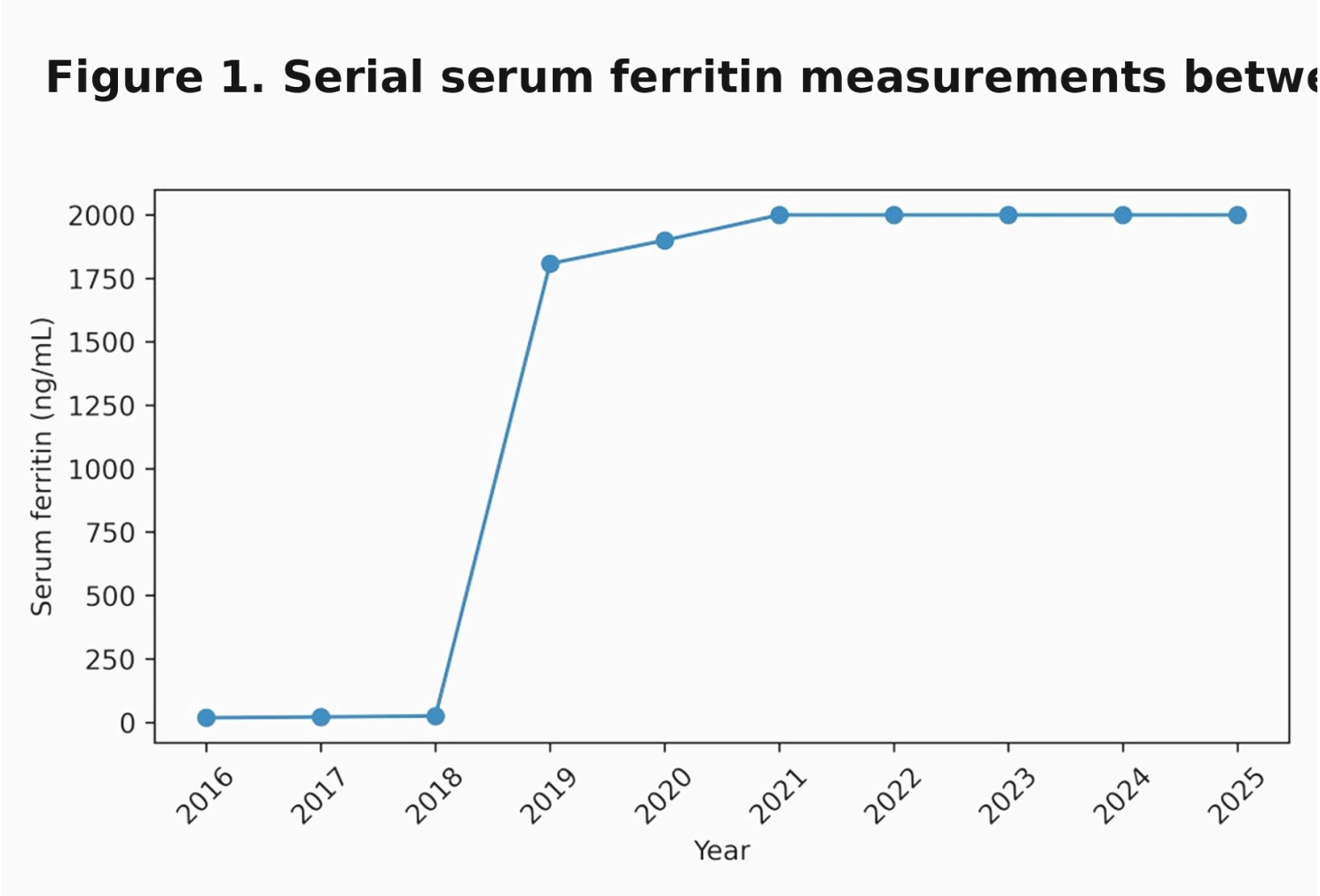


Figure 1

See image above for figure legend.

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