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‘First report of liver transplantation in Blau syndrome’

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Introduction

- Blau syndrome is a **rare autosomal dominant** inflammatory **granulomatous** disease caused by mutations in the *NOD2* gene, classically presenting in childhood.
- Hepatic manifestations are recognized including cholestasis and granulomatous liver disease.
- We describe a **novel *NOD2* gene mutation** in an adult presenting with decompensated granulomatous liver disease
- He required an **orthotopic liver transplant**, the **first** reported in this syndrome.
- Furthermore, we **appraise the effectiveness** of antibody therapies in halting disease progression in this syndrome

Case Report

Our patient initially presented with juvenile idiopathic arthritis and uveitis at the age of three years. He remained well until the age of 21 years, when he presented with cholestatic liver enzyme derangement, ascites and weight loss. Imaging suggested portal hypertension and a liver biopsy revealed epithelioid granulomas with no central necrosis and multinucleate giant cells with peri-venular and peri-portal fibrosis (Figure 1).

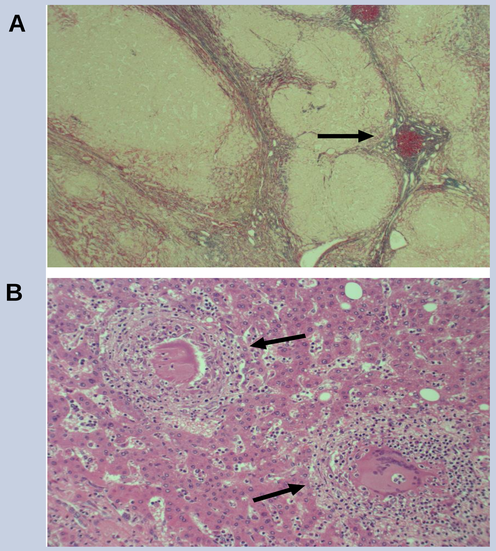

Figure 1: Liver biopsy results showing broad fibrous septa with small nodule formation (A) and non-necrotizing granulomatous inflammation (B).

Chronic liver screen and mycobacterial testing was negative. Around this time his daughter developed polyarthritis, uveitis and hepatosplenomegaly at the age of 4 years. She was diagnosed with Blau syndrome after genetic testing revealed the hitherto unreported pathological variant, c.1471A>C, p.(Met491Leu), in the NOD2 gene (Figure 2).

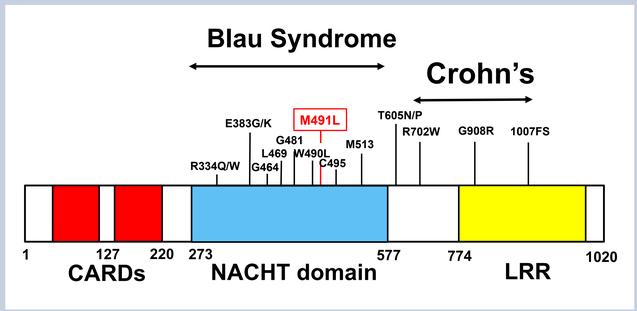

Figure 2: Distribution of the mutations in the NOD2 gene. Our patient’s novel mutation is highlighted in red within the central NACHT domain

Genetic testing confirmed the same mutation in her father. At the age of 31, despite immunotherapy he developed cirrhotic complications including recurrent oesophageal bleeding and spontaneous bacterial peritonitis. He subsequently received a Donation after Circulatory Death (DCD) graft in March 2019. Progress following transplantation was satisfactory and immunosuppression consisted of Tacrolimus, Azathioprine and Prednisolone. Three months later he was treated for septic complications from ischemic cholangiopathy. Imaging revealed a degree of hepatic artery stenosis and bile duct stricturing, thought to be ischemic in nature. His liver biopsy showed evidence of disease recurrence in the graft (hitherto unreported), although the dominant pathology and cause of graft failure was ischaemic cholangiopathy. Following his initial grafting he is awaiting re-transplantation.

Review of Antibody Therapies in Blau Syndrome:

Of 84 Blau patients treated with antibody therapy, 5 hepatic cases responded to anti-TNF therapy, with promising results if instigated before decompensation occurs (Figure 3, Table 1).

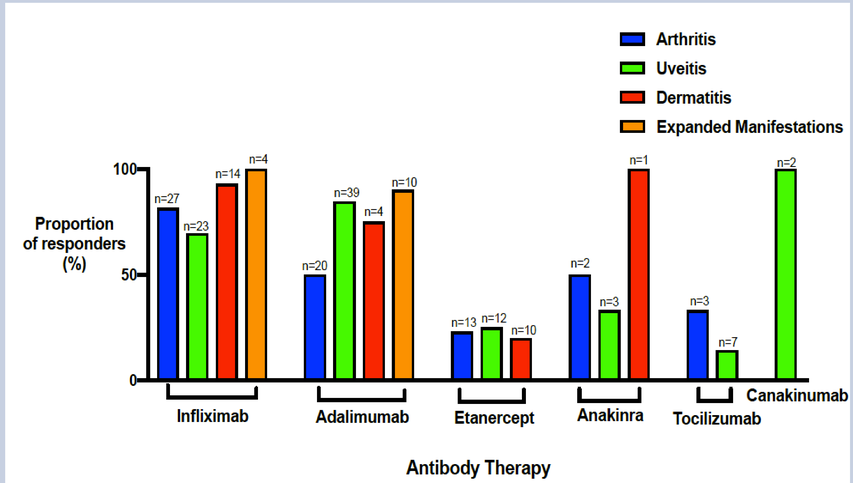

Figure 3: Histogram showing the proportion of responders to individual antibody therapies and their effectiveness in Blau syndrome

Reference	Age at diagnosis (years)	Liver disease	Biopsy	NOD 2 mutation	Antibody therapy	Response
Martin TM et al 2009	8	Hepatic granulomas	YES	R334Q	Infliximab	Clinical response
Chauhan K et al 2014	2	Hepatic granulomas	YES	E498G	Adalimumab	Improvement in biochemistry and elastography
Rosé CD et al 2015	N/A	Hepato-splenomegaly	N/A	R334Q	Infliximab	Clinical response
Rosé CD et al 2015	N/A	Hepato-splenomegaly	N/A	E383K	Infliximab	Clinical response
Dziedzic M et al 2017	2	Hepato-splenomegaly	N/A	P268S	Adalimumab	Clinical response

Table 1: Antibody therapy in five cases of Hepatic Blau Syndrome

Conclusion

We report the **first** case of **liver transplantation for Blau syndrome**, in an adult case of Blau syndrome with a **novel *NOD2* mutation**.