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HYPERINFLAMMATION AND BLINDNESS. SCREENING FOR ROSAH SYNDROME

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ABSTRACT

In 2019, ROSAH syndrome (retinal dystrophy, optic nerve oedema, splenomegaly, anhidrosis, and headache) was identified in five families, attributed to a mutation in the *ALPK1* gene. Subsequently, in 2022, it was classified within the spectrum of autoinflammatory diseases with multisystemic involvement. Evidence has demonstrated that this genetic mutation induces hyperactivation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) inflammasome pathway, and the clinical phenotype of 27 patients has been documented.

We present the case of a patient who experienced an acute presentation characterized by anaemia, thrombocytopenia, and mild renal and hepatic dysfunction. Furthermore, this article underscores the remarkable therapeutic efficacy of interleukin 6 (IL-6) blockade and provides a detailed account of the clinical progression of the various organs and systems affected by the disease.

KEYWORDS

ROSAH syndrome, inflammation, optic nerve oedema, *ALPK1* gene, tocilizumab

LEARNING POINTS

- ROSAH is a syndrome that includes retinal dystrophy, optic nerve oedema, splenomegaly, anhidrosis and headache.
- So far it has only been reported in five families who have a mutation in the *ALPK1* gene.
- Patients can improve dramatically on treatment with an interleukin 6 inhibitor.

INTRODUCTION

In 2019, ROSAH syndrome (retinal dystrophy, optic nerve oedema, splenomegaly, anhidrosis, and headache) was described in five families as a result of a mutation in the *ALPK1* gene[1]. In 2022, it was able to be classified as part of autoinflammatory diseases with multisystem involvement, it

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has been shown that this mutation confers hyperactivation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) inflammasome pathway and the phenotype of 27 patients has been described[2].

We report a case of a patient who presented acutely ill with anaemia, thrombocytopenia, and mild renal and hepatic failure.

CASE DESCRIPTION

The patient is a 35-year-old male with a history of bilateral blindness and low body weight since childhood. He presented with a seven-day history of anorexia, generalised weakness, fatigue, loss of bowel control and recurrent falls. He was cachectic, lethargic and disoriented with fluctuating behavioural symptoms notable for 3/5 motor strength in the arms and 2/5 in the legs. On examination the skin was pale with conjunctival jaundice and the mucous membranes were dry. His temperature was 36.5°C with a heart rate 70 beats per minute; his blood pressure was 100/60 mmHg, respiratory rate 24 breaths per minute and oxygen saturation 96%. His haemoglobin level was 3 g/dl, and he received three units of packed red blood cells over six hours. He was severely ill and required fluid resuscitation and correction of his severe folate deficiency with transfusion. The severity of his condition prompted an abdominal computerized tomography (CT), which revealed an enlarged liver and spleen. CT and magnetic resonance imaging (MRI) scans of the brain were both normal.

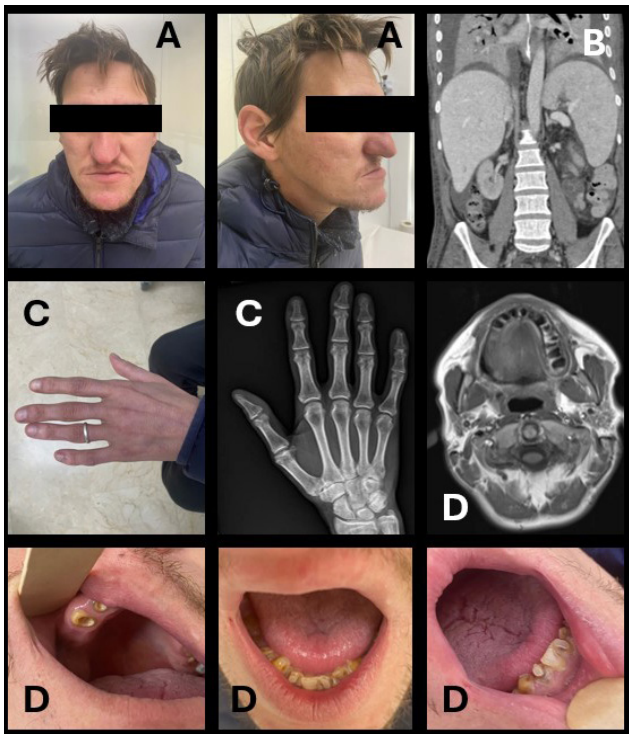


Figure 1. A) Typical rough facial features can be seen in these photos; B) CT scan from patient demonstrating hepatosplenomegaly; C) Inflammatory arthritis and bone deformity in interphalangeal and metacarpophalangeal joints; D) These images show dental alterations, which include short dental roots and loss of enamel from the tooth surface. In the MRI you can see edentulous and taurodontism areas. Oral dryness is typical, contributing to the formation of cavities and is similar to Sjögren's syndrome.

While in hospital his renal function continued to deteriorate, and he required haemodialysis; C3 glomerulonephritis was found on renal biopsy. The patient had been blind since childhood and the cause was unknown. He also had difficulty sweating, migraines accompanied by photophobia, occasional episodes of inflammatory arthralgia in the knees and interphalangeal joints of the hands. He often had episodic chills but no objective fever. The patient had thick saliva and multiple cavities along with tooth loss since adolescence *(Fig. 1)*.

The combination of retinal atrophy and sustained optic nerve oedema *(Fig. 2)*, splenomegaly, anhidrosis and headache suggested the possibility of ROSAH syndrome, which was confirmed by genetic exon 9 sequencing of the *ALPK1* gene, revealing the c.710C>T p.(Thr23Met) mutation. This is a missense mutation, and is the commonest alteration found in ROSAH syndrome[3].

The patient was treated with tocilizumab, an interleukin 6 (IL-6) inhibitor[1], on which his general condition improved; he had less asthenia and joint pain, fewer headaches and absence of fever. He also showed ophthalmological improvement with an enhancement in visual acuity. After one year of treatment with tocilizumab the patient leads a normal life, has moderately reintegrated into his previous routine and tolerates dialysis sessions much better. Additionally, he has gained weight and has not experienced any further vitamin or nutritional deficiencies.

DISCUSSION

Our case corresponds with the index case of the family, being the first affected individual in their family and the first case described in Spain. It is not related to the other described families[2]. Since we knew about the mutation and the patient had two children aged 9 and 11 both were studied, presenting the mutation without any associated clinical symptoms at that time. In the study published by Kozycki et al.[2], the effectiveness of various treatments such as tumour necrosis factor or interleukin-1 blockers was discussed. However, it was the blockade of IL-6 with tocilizumab that achieved the greatest improvement in the ophthalmologic component, leading the authors to propose it as the best option for these patients. This, along with the safety and efficacy demonstrated by tocilizumab in dialysis patients during the COVID-19 pandemic[4], led us to use it for this patient. We believe that the improvement observed at the ocular, articular and asthenia levels, as well as the recovery of sweating, is similar to what has been described in the literature, although further studies are needed to confirm this. However, there has been no renal improvement. Notably, no glomerular alterations have been reported in other patients with ROSAH syndrome, nor have complement pathway abnormalities like those observed in our patient. We believe this may be related to the patient's multiorgan failure rather than the ROSAH syndrome itself.

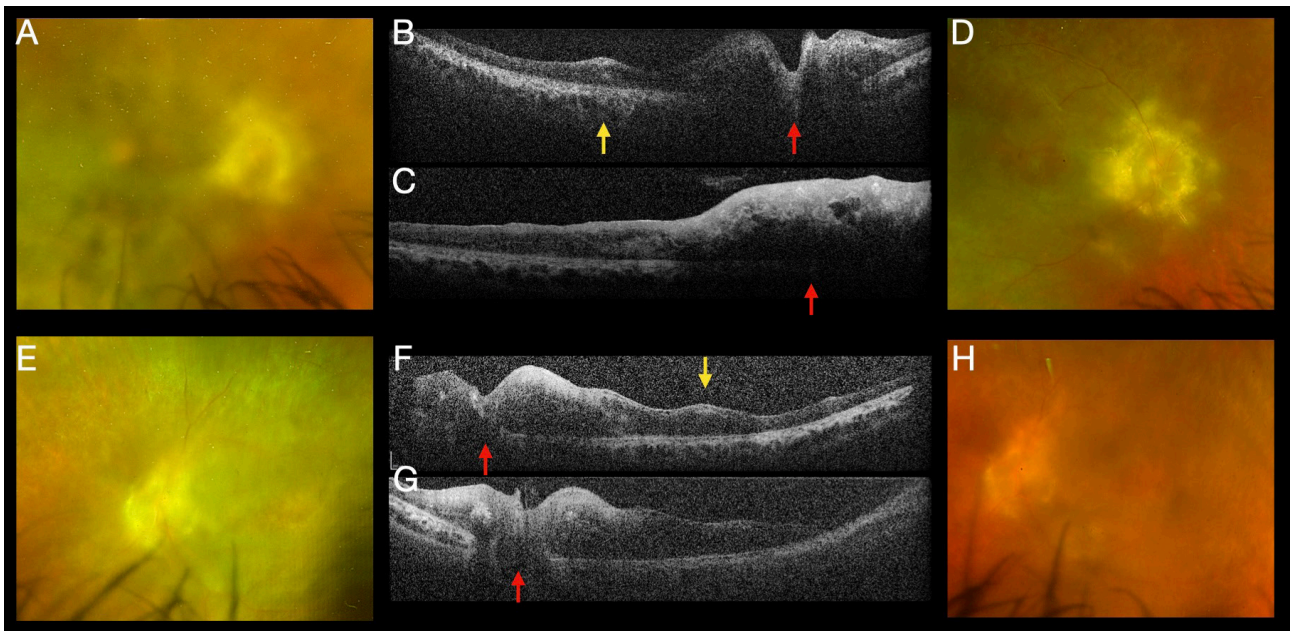


Figure 2. A) Colour fundus photography (CFP) of the right eye (OD) before treatment. The image is blurry due to media opacification showing a chronic optic nerve swelling with secondary fibrosis, filiform vessels and atrophy of retina, and retinal pigment epithelium (RPE) without bone-spicule-like pigment deposition; B) Optical coherence tomography (OCT) of the OD at presentation disclosing a severe optic nerve swelling (red arrow) and an area of increased retinal thickness corresponding to the foveal region, suggestive of macular oedema (yellow arrow), in an otherwise atrophic retina; C) OCT of the OD at the last follow-up. The optic nerve swelling persists (red arrow); however, it seems there is a decrease of the retinal thickness suggesting an improvement of the macular oedema; D) CFP of the OD after treatment initiation with a clear view of retinal structures (in part due to cataract surgery) showing a chronic optic nerve swelling, fibrosis and peri-optic nerve atrophic foci, filiform vessels and lack of bone-spicule-like pigment deposition; E) CFP of the left eye (OS) before treatment revealing optic nerve swelling and fibrosis, and an atrophic retina and RPE with filiform vessels and no pigment deposition; F) OCT of the OS before treatment disclosing optic nerve swelling (red arrow) and an area of probable macular oedema (yellow arrow); G) OCT of the OS post treatment initiation showing an improvement of the retinal thickness with absence of macular oedema and persistent optic nerve swelling (red arrow); H) CFP of the OS at the last follow-up, revealing persistence of the optic nerve swelling and fibrosis.

The clinical presentation of this patient can be considered as ROSAH syndrome with typical manifestations[1,5] except for the MRI alterations, which are common in patients with migraines. Our patient did not present any evident malformation, although we are unable to determine the exact reason for this. However, he presented with a severe manifestation due to folate deficiency; we suggest that the malabsorptive syndrome may be due to ROSAH syndrome, as observed in other patients, and may be the cause of the patient's folic acid deficiency, leading to hypovolaemic shock and multiorgan failure. Digestive involvement is known to occur in other syndromes in which NF-KB is affected, such as NEMO (NF-KB essential modulator) deficiency syndrome C terminal deletion, which also presents with malnutrition and anhidrosis[6].

ROSAH syndrome, along with an inflammatory condition, causes a ciliopathy that may contribute to malabsorption. We propose that the combination of these factors is behind the severe clinical presentation of this patient as well as the original cause of the blindness and the inflammatory episodes he has had since childhood.

The severity and presentation suggest that this patient's inflammatory response may have been amplified by enhanced signalling of the NF-KB pathway. It has also been shown that patients with mutations associated with ROSAH syndrome have a constitutive increase in *STAT1* activity levels as well as elevated levels of interferon-1, which may have further increased the patient's inflammatory role, amplifying multiorgan failure during an inflammatory stress situation such as hypovolaemic shock that led to hospitalisation.

CONCLUSION

The case we present reinforces the idea that ROSAH syndrome goes beyond ophthalmological involvement and that gain-of-function mutations in the NF-KB pathway generate a situation of systemic inflammation due to the Thr23Met mutation in exon 9 of *ALPK1*.

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