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Blau Syndrome: A case report

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ABSTRACT
Blau syndrome is an autosomal dominant granulomatous disorder caused by mutations in the pattern recognition receptor NOD2, presenting in very early childhood with the triad of arthritis , uveitis and dermatitis. Due to similarity in clinical presentation to JIA , the diagnosis can be delayed . We report a case here of a young female patient who became symptomatic at the age of 2 years but was diagnosed as Blau's syndrome eleven years later.

I. INTRODUCTION

Blau syndrome (BS) is a rare autosomal dominant autoinflammatory granulomatous disorder resulting from mutations in NOD2 , the pattern recognition receptor and the responsible gene has been identified in the caspase recruitment domain gene CARD15/NOD2.

Described by E Blau and D Jabs in 1985 , it is characterised by the classical triad of arthritis , uveitis and dermatitis presenting in early childhood , usually in the first 4 years of life.It can be mistaken for juvenile idiopathic arthritis on account on account of the similarity in clinical manifestations (1,8).

II. CASE REPORT

A 16 years old girl , born prematurely in 2006 of a non- consanguineous marriage had delayed developmental milestones recurrent respiratory infections, and a failure to thrive from the age of 2 months . She was admitted and evaluated at different hospitals and at the age of 1 year was diagnosed as Protein energy malnutrition – kwarshiokar with icthyosis vulgaris. She was thereafter on ayurvedic treatment for a year.

At 2yrs of age she was noted to have additive recurrent swelling of various joints associated with pain. There were episodes of fever associated with joint pains . Her APRs were elevated. She was diagnosed to have Juvenile idiopathic arthritis and initiated on steroids and methotrexate with improvement in her joint symptoms. In addition was also noted by the mother to have diminution of vision and was evaluated by ophthalmology and diagnosed as anterior uveitis with vitreous detachment with bilateral diminution of vision .

Over the next 2-3 years , she had frequent hospital admissions for infections of the respiratory tract , continued to have flares of joint symptoms while on methotrexate and steroids and in 2016 , developed vitreous haemorrhages in both eyes with loss of vision . She was then initiated on anti TNF adalimumab for a year .

On account of recurrent respiratory tract infections and cough , she underwent HRCT thorax in 2017 which was reported as non specific interstitial pneumonia (NSIP). Work up for pulmonary TB was negative .At this point, she was referred to a paediatric rheumatologist who evaluated her in detail and on the basis of arthritis , bilateral uveitis , NSIP , suspected the diagnosis of Blau's syndrome which was confirmed by genetic analysis : NOD gene mutation positive;Exon-4 clinical variant. A PET-CT at this point revealed mediastinal and lung nodules plus diffuse minimal skeletal muscle uptake and uptake in multiple joints . Autoimmune work up including RF, ACCP and ANA was negative . Due to financial constraints , anti TNF therapy could not be administered and the patient was switched over to mycophenolate mofetil and low dose glucocorticoids with good clinical response and improvement in

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pulmonary function tests and she continues to be clinically stable till date .

III. DISCUSSION

Blau Syndrome is an autosomal dominant inherited granulomatous disorder characterised by the classical triad of papuloerythematous rash , recurrent uveitis with multifocal choroiditis and symmetric cyst -like or boggy polyarthritis (2, 10). This rare disorder was first described by Edward Blau in 1985 in 11 members of a four generation family. The disease is caused by a mutation in the NOD2 gene which has been mapped to the chromosome 16q12.2-13 and three missense mutations (R334Q, R334W and L469F) were identified in the region encoding the NACHT domain of the CARD15 / NOD 2 gene (2,6,8). R334Q and R334W have been found to be the most prevalent mutations (5,7). The NOD 2 gene encodes a protein in the NLR (NOD like receptor) family which regulate apoptosis and activation of nuclear factor kappa β (NF-κβ) .In BS , the activation of NF-κβ is 4 times higher and this causes augmented inflammatory gene transcription, a dysregulated immune system and multisystem granulomatous inflammation (8) .

There are many similarities clinically between BS and early onset sarcoidosis(EOS). Many patients with EOS also demonstrate mutations in NOD2 / CARD15 on genetic analysis. Hence it had been initially proposed by some that EOS and BS represent the sporadic and familial forms of the same disease. It has now been proposed to classify these patients as (i) familial BS (with a family history) (ii) sporadic BS (due to denovo mutations) and (iii) EOS (those with clinical features of sarcoidosis but without autosomal dominant transmission and mutations in NOD2 / CARD15) (2). Our case would then be categorized as sporadic BS as she had a genetically proven mutation but with absent family history .

In most patients , as in our case , the onset of disease is early , before 3-4 years of age with arthritis being the most common manifestation , appearing in the first decade of life. This initial presentation of the disease as arthritis sans skin or ocular manifestations can lead to it being diagnosed as JIA as in our patient (2). In a Japanese cohort of 50 patients with BS and confirmed NOD 2 mutation, fever was an important clinical feature occurring in half the cohort , 63% of patients had rash (scaly erythematous plaques / lichenoid papules / erythema nodosum) as the first symptom and in most cases the rash appeared before 4 years of age . The majority of patients had inflammatory arthritis (polyarticular / oligoarticular) and arthritis occured after the rash . 76% of patients had both anterior and posterior uveitis and 7 patients in the cohort had visual loss . (4)

Our case also had very early onset disease with cutaneous manifestation at the age of 1,which was diagnosed as Icthyosis vulgaris then fever , arthritis and visual manifestations and later at the age of 11 was found to have developed interstitial pneumonitis . A case report by Masel et al describes a patient with Blau presenting with icthyosis resembling icthyosis vulgaris which was subsequently biopsy proven to show granulomas .(9) . Similarly , there has also been reported interstitial pneumonitis and granulomatous lymphadenitis , usually features of adult onset sarcoidosis , in a patient with CARD 15 mutation positive familial BS (10).

There are case reports of atypical cases of BS with involvement of other organ systems such as granulomatous renal and liver involvement . granulomas in the lymph nodes, intestine , parotid glands , painful leg ulcers , cranial neuropathies and loss of hearing .(2)

The treatment of BS remains challenging and there is no specific cure. Various therapies have been tried including steroids and steroid sparing agents such as methotrexate , thalidomide , cyclosporine , mycophenolate , tofacitinib , anti IL-1 and TNF agents. Anti TNF agents are used when the disease is not controlled by steroids and other steroid sparing drugs . In the Japanese cohort , anti TNF therapies were particularly useful in treating and stabilizing ocular manifestations .(3,8) . In our patient , by the time she was initiated on adalimumab , she had already sustained permanent visual loss . She was subsequently commenced on mycophenolate and the disease has been well controlled on low dose glucocorticoids and mycophenolate .

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