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Case Report

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A Case of Growth Retardation in a Child with STING Associated Vasculitis

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Abstract

This is a case report of a 6 year old Caucasian male presenting for growth retardation. The child exhibited stunted growth, along with interstitial lung disease, 2 year history of poly-articular joint pain and peripheral erythema associated with vasculitic rash upon further investigation. He was diagnosed with SAVI syndrome; an autosomal dominant, type 1 interferonopathy with interstitial lung disease, systemic inflammation, and peripheral cutaneous and joint involvement.

Introduction

Nowadays, the identification of new monogenic disorders was permitted by the new advances in genomic techniques. These monogenic auto inflammatory diseases can involve perturbations in signaling by the transcription factor sush as NF-κB, or can involve ubiquitination, cytokine signaling, protein folding, or type I interferon production which is the case in SAVI [1].

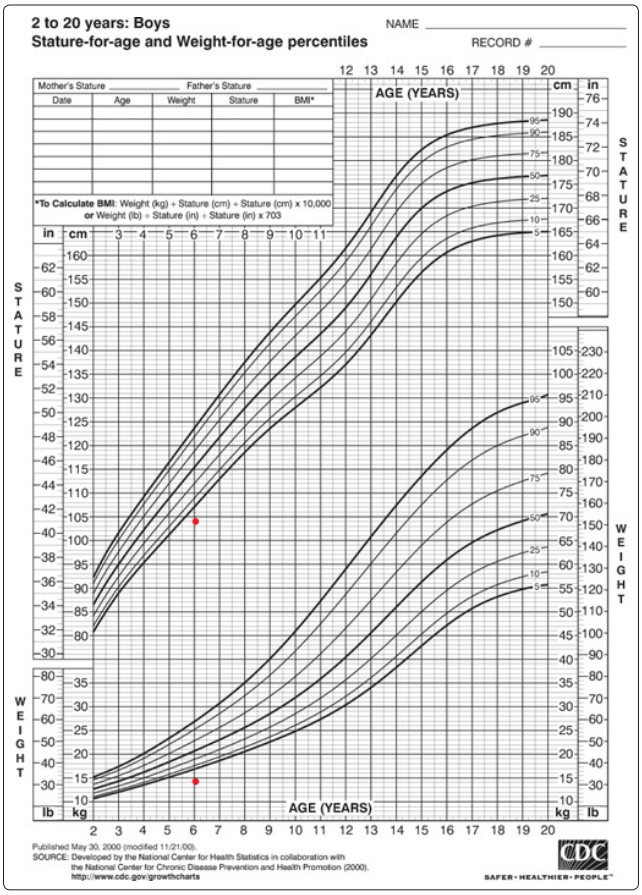
SAVI Syndrome is characterized by cutaneous vasculitis associated with peripheral rash over the extremities mainly the lower ones [2]. Other manifestations include fever, interstitial lung disease, and systemic inflammation as early as the 8th week of age. Also, early onset of lupus-like manifestations associated with lung involvement should raise the suspicion of this disease [3]. The inflammatory component of SAVI has a physiopathology similar to the autoinflamatory conditions that involve the different agents of the immune system [4]. Laboratory evaluation most commonly reveals features such as positive ANA titers, as well as elevated IgG and IgA [5]. SAVI syndrome is the only known type 1 interferonopathy where lung involvement is the most common and major feature [6]. The underlying etiology is an autosomal-dominant, gain-of-function mutations in the TMEM173 gene. "TMEM173 encodes for the STING protein, which is an adaptor molecule linking sensing of foreign (viral and bacterial) DNA to the production of type 1 IFNs as part of the innate immune response" [5]. The result is a constitutive activation of STING and up-regulated type 1 IFN production. Type I IFN signaling control cellular reponse by regulatory pathways that are incriminated in the innate and adaptive immune response [7]. The STING protein can be found in alveolar macrophages, bronchial epithelium, and alveolar type 2 pneumocytes, which explains the involved lung pathology seen in SAVI. Moreover, STING protein has direct action on endothelial cells leading to inflammation and coagulation cascade. Therefore, the TMEM173 mutations are thought to conduct chronic vessel endothelium inflammation, thus resulting in vasculitic rash ad vaso-occlusion as seen in SAVI [5]. Due to the advancement of sequencing, as well as the awareness of the presence of diseases such as SAVI, Volpi S et al expect that more patients seen by pediatric rheumatologist will be diagnosed with new type I interferonopathies [8].

Treatment of SAVI remains challenging, with reports of limited response to steroids, disease-modifying ant rheumatic drugs, and biological therapies [9,10]. In one patient report, there was isolated improvement in interstitial lung disease following pulse therapy with methylprednisolone and mycophenolate mofetil. Moreover, Janus kinase inhibitors offer hope in their action of blocking type 1 IFN signaling, despite constitutively activated STING. "Baricitinib has shown benefit in adult patients with a range of inflammatory conditions, but there are limited pediatric data" [5]. Many cases are self-limited but some cases can have a recurrence of the disease or a progression to a chronic condition [2].

Case Presentation

The patient reported is a 6 year old Caucasian boy, born term by normal vaginal delivery, having Raynaud's Syndrome, and no other medical or surgical history, presenting for growth retardation. The child was at the lower 5th percentile of his growth chart, with a weight of 14 kg and height of 104 cm. (Graph 1) He had negative family history of autoimmune disease, with no social history of sick contact, travel, or exposure to toxic chemicals. There was no evidence of abuse, neglect, or malnutrition. The parents were not consanguineous.

Upon further investigation, we discovered that the patient had a long history of migratory poly-articular joint pains mainly in the small joints (wrists and fingers) lasting for 2 years, and a more recent history of right knee pain lasting for 5 days as well as bilateral pain and tenderness of the wrists, DIP and PIP joints of the hands, associated with peripheral extremity rash of the hands, legs, and cheeks for the past 4 months. His articular pain is associated with swelling and erythema.



Graph 1: Patient's Male Growth Chart Plot

On physical examination, the patient had varus deformation of his fingers, with edema, and erythema of the PIP and DIP joints of the hands. He also had a vasculitic rash of the cheeks, hands and legs. There is petechial on his nose, ears and legs bilaterally. Capillary refill time was greater than 3 seconds in the 3rd right and left toes, as well as the 5th toe. His neurologic examination was within normal limits, there were no signs of mental retardation.
Laboratory evaluation was as follows:

A CBC was done and turned out to be normal

Table 1: Laboratory workup

ESR at 1 hour	49	**ASO**	411
ESR at 2 hours	85	**RF**	44.2
Fibrinogen	3.22 g/L	**IgA**	12
ANA	1/640	**Anti- transglutaminase IgA**	15
IgF binding protein 3	1380	**Anti-transglutaminase IgG**	0.2
C3	1.22 g/L	**IgF 1 Somatomedina C**	17 mg/L
C4	0.15 g/L	**Vitamin D**	84.8 mg/ml
Albumin	3.9 g/dL	**Total protein**	8.4 g/dL
		TSH	2.37 mIU/ml

The most important lab finding to note were the significant elevated level of ESR: 85 at 2hours(Table 1). Moreover, cANCA was negative, cold agglutination test was negative, and indirect coombs was negative. However, direct coombs was weakly positive, and pANCA was positive.

Imaging performed included an X-ray of the left forearm and hand, a chest radiograph, as well as a thoraco-abdominal CT scan with contrast material. The results were as follows:

Bone age was determined to be at age 3 years, for a chronological age of 6 years and 2 months, according to the Atlas of Roo and Shroder. (Image 1)

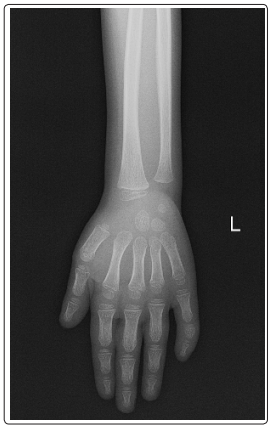


Image 1: Left forearm and hand X-ray

A chest x ray was done and has showed peri-bronchial alteration, as well as diffuses parenchymal infiltrates, mainly interstitial. (Image 2)

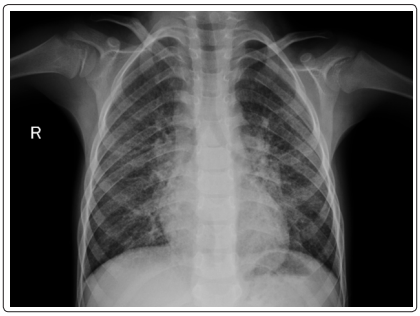


Image 2: Chest X-ray

Chest CT scan showed septal peri-bronchovascular, inter and intralobular, diffuse thickening and fibrotic lineal infiltrates of the two bases, predominantly on the left side. Homogeneous enhancement of the major vessels. (Image 3 and 4)

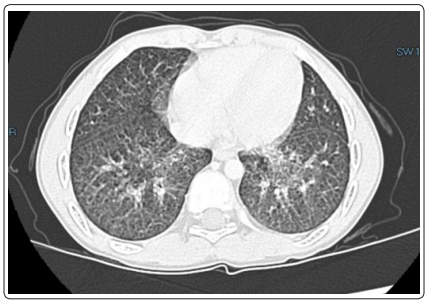


Image 3: Chest CT scan

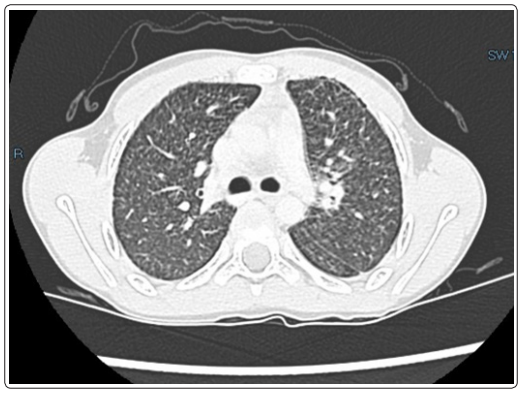


Image 4: Chest CT scan

CT angiography has shown: some small ganglionic formations in bilateral axillaries regions. Lymph nodes in clusters at the level of the medium mediastinum: hilar lymphadenopathy (14 mm) and 18mm at the Lodge of Barety and 18 mm. No pleural or epicardial effusion. Intrasplenic hypodensity of 5 to 6 mm. Discreet thickening and irregularity of the peribronchovascular tissue at the infrahilar level and the bronchial tubes of the basal pyramid. Presence of lymphatic impairments with peribronchovascular and Centro lobular distribution of micro nodules in a diffuse manner.

Echocardiography was performed along with the series of investigations, and it proved to be within normal limits, along with a normal abdominal ultrasound.

The diagnosis of sarcoidosis has to be ruled out. The patient was treated with short term corticosteroids and was seen by a rheumatologist that has added Imuran to his treatment without any improvement of his condition. Afterwards, he was admitted to the hospital in order to receive bolus steroids without a significant improvement as well. The diagnosis of SAVI was suggested as a diagnosis of exclusion and has been confirmed with a genetic testing (mutation in TMEM173).

To conclude, this patient with growth retardation was diagnosed with SAVI syndrome; a disease with significant impact on both patient and family due to high morbidity and mortality. In our patient, growth retardation, joint pains and cutaneous manifestations dominated, however the fearful characteristic of disease remains the lung involvement which holds greatest debilitating health risks, which are the leading cause of death in such patients [9, 10].

Finally, the auto-inflammatory diseases such as SAVI syndrome should be kept in mind as a differential diagnosis in children with growth retardation.

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