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Rare Association of Adult Onset Still's Disease with Autoimmune Thyroid Disease: A Case Report

Karthik V. Badarayan[1], Jitendra S. Oswal[1], Sandeep Kansurkar[2], Rahul Jahagirdar[1]

[1] Department of Pediatrics, Bharati Vidyapeeth Medical College and Hospital, Pune, India.

[2]Department of Clinical Immunology and Rheumatology, Bharati Vidyapeeth Medical College and Hospital, Pune, India.

Abstract

Adult-onset Still's disease (AOSD) is an uncommon inflammatory condition presenting with high grade fever, arthralgia, skin rash, and leukocytosis. Autoimmune thyroid disease (AITD) is commonly seen in females in their third to fifth decade and usually missed to screen in other autoimmune diseases. In this study, the case of a 17-year-old female patient from Pune is reported who presented to Bharati hospital in November 2020, with a six-month history of high-grade fever, arthritis, and elevated acute phase reactants along with hypothyroidism. She was diagnosed with AOSD (based on Yamaguchi criteria) and AITD with positive anti-thyroid peroxidase (anti-TPO) antibodies. She responded well to oral steroids and thyroid supplements. This case draws attention to the rare association between AOSD and AITD.

***Key Words*:** Autoimmune thyroiditis, Children, Hypothyroidism, India, Yamaguchi criteria.

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Corresponding Author:

Jitendra S. Oswal, MD, Professor of Pediatrics, Pediatric Rheumatology Clini, Department of Pediatrics, Bharati Vidyapeeth Medical College and Hospital, Pune, India.

Email: jsoswal@gmail.com

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1- INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder that is characterized by high-grade fever with an evanescent, non-pruritic maculopapular rash, arthritis, and multi-organ involvement. Still's disease was first described by Sir George Frederic Still, an English physician, who in 1897 published a monograph titled "A Form of Chronic Joint Disease in Children" where he described 22 children with signs and symptoms of the disease, currently known as systemic-onset juvenile idiopathic arthritis (1). There is no single diagnostic test for AOSD and the diagnosis is mostly based on clinical and laboratory criteria and excluding other autoimmune diseases, neoplasms, and infections. AOSD usually presents in older children and is similar in presentation to systemic juvenile idiopathic arthritis, making the differentiation difficult. Among the several diagnostic criteria developed over the years, Yamaguchi's criteria have been the most widely used due to its higher sensitivity (96.2%), and specificity (92.1%) (2).

Autoimmune thyroid disease (AITD) is a condition affecting 1% to 5% of general population, especially seen in women during their third and fifth decades of life (3). Common AITD representations include Graves' disease and Hashimoto's thyroiditis. Diagnosis of AITD is based upon clinical manifestations and laboratory results, including abnormal levels of thyroid hormone and antibodies against thyroid peroxidase (TPO) and thyroglobulin. In 98% of cases, AITD is positive for either antibody, so a negative test may rule out AITD (4).

2- CASE REPORT

A 17-year-old female patient was brought to Bharati Hospital, Pune in November 2020 with a 6-month history of high grade fever spikes (maximum body temperature documented up to 103^{o} F) along with multiple swellings in her neck and axillae. In addition, in the past three months, she had developed intermittent swelling and pain in multiple joints in both of her hands and wrists. On examination, she was found with multiple enlarged lymph nodes (with the largest measuring 1x2 cm) which were firm, non-tender, and mobile on the both sides of cervical, axillary, and inguinal regions. A solitary, non-tender, mobile, midline neck swelling measuring 2x5 cm was noticed. Both of the wrist joints along with bilateral metacarpophalangeal joints were swollen and tender. The rest of her systemic and musculoskeletal examination was unremarkable. The following differential diagnosis were considered: Pyrexia of unknown origin, probably due to tuberculosis, human immunodeficiency virus (HIV) infection, brucellosis, malignancy, or any systemic autoimmune disease along with probable thyroid disease. Her serial laboratory investigations are shown in **Table.1**.

The absolute neutrophil count, erythrocyte sedimentation rate, C-reactive protein, and ferritin were above normal. Peripheral smear for malaria was negative. Sputum and gastric aspirate for acid-fast bacilli and cartilage-based nucleic acid amplification test were negative. Computerized tomography of the chest and ultrasonography of the abdomen did not show any abnormality. Blood and urine cultures were sterile. Thyroid function test showed raised thyroid stimulating hormone with low free triiodothyronine (fT3) and thyroxine (fT4), suggesting hypothyroidism. Anti-TPO antibody titer was strongly positive, suggesting AITD. She was started on thyroxin at 50 mcg/day and her thyroid function tests normalized after four weeks. The serological tests for HIV and Brucella were negative. Excision biopsy of the right axillary lymph node suggested reactive lymphadenitis. Bone marrow aspiration and biopsy reported reactive marrow with no atypical cells or blasts. Positron Emission Tomography

and Computed Tomography (PET-CT) scan of her whole body showed weakly metabolic lymph nodes in the neck, axillae, and mediastinum with hypermetabolic spleen and bone marrow. As her high-grade fever spikes continued, differential diagnosis of evolving lupus, sarcoidosis, adult-onset still's disease, or Immunoglobulin G4-related disease were considered. Anti-nuclear antibody, anti-dsDNA antibody, and RF tests were negative. Serum angiotensin-converting enzyme level and immunoglobulin levels were within normal limits. AOSD was diagnosed using Yamaguchi criteria, fulfilling three major (fever > one week, arthralgia > two weeks, and leukocytosis with >80% neutrophils) and two minor (lymphadenopathy, negative anti-nuclear antibody, and negative rheumatoid factor) criteria. Oral prednisolone at 1 mg/kg/day was initiated after which her fever and arthritis disappeared within 24 hours of treatment. On follow-up at four weeks, she remained asymptomatic and her acute phase reactants showed normalizing trend.

Table-1: Laboratory investigations.

Laboratory parameters	At presentation	After 4 weeks	After 4 weeks of prednisolone
Hemoglobin (gram %)	10	7.7	8.9
Total leukocyte count (/cubic millimeter)	15500	12600	16200
Neutrophils (%)	87	80	75
Absolute neutrophil count (/cubic millimeter)	13485	10080	12150
Lymphocytes (%)	13	9	22
Platelets (/cubic millimeter)	426000	531000	510000
CRP (mg/dl)	77.67	82	18
ESR (mm in 1st hour)	85	105	29
Ferritin (ng/ml)	6790	12264	1045
ANA by IF	-	Negative	-
Rheumatoid factor	-	Negative	-
ACE level (U/L)	-	58	-
TSH (mIU/ml)	80.18	9.8	-
fT3 (pg/ml)	0.57	1.1	-
fT4 (pg/ml)	4.09	5.3	-
anti-TPO antibody (IU/mL)	>1000	-	-

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ANA: Anti-nuclear antibody by immunofluorescence method, ACE: Angiotensin converting enzyme, TSH: Thyroid-stimulating hormone, fT3: free tri-iodothyronine, fT4: free thyroxine, Anti-TPO: Anti-thyroid peroxidase antibody.

3- DISCUSSION

The association between AITD and AOSD has not been previously reported in Indian literature. However, the association of AITD with rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome has been reported (5), which implies the relation of systemic autoimmune disease related to AITD. In the case of this study, a coincidental link could not be ruled out. AOSD has a prevalence estimated at less than one case per 100,000 people. Females appear to be more frequently affected than males (6). So far, no familial trend has been reported, but studies have described an association with human leukocyte antigen (HLA) alleles, namely DR4, B17, B18, B35, DR2, DR5, and DQ1 (7). Neutrophil and macrophage activation remains a hallmark of AOSD, and is mediated by tumor necrosis factor- alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-18 (IL-18) (8). Over the past

decade, the potential role of T-helper (Th) cells in the pathogenesis of AOSD has been gaining attention. Chen et al. found higher amounts of interferon-gamma (IFN-γ) producing Th cells and higher Th1/Th2 ratios in the peripheral blood of AOSD patients compared to healthy controls (8). Many cytokines have been implicated in the pathogenesis of AOSD, including TNF-α, IL-1β, soluble IL-2 receptor, IL-6, IL8, IL-17, and IL-18. Correlation of high serum ferritin and neutrophil count in active disease is suggested by high levels of IL-18. IL-1β modifies thyroid epithelial tightness through altering the expression of junctional proteins, promoting the progression of autoimmune diseases like rheumatoid diseases, AITD, and multiple sclerosis (MS) (9). The interferon-gamma expresses major histocompatibility complex class II molecules by acting as antigen-presenting cells to activate an autoimmune response. Hence, both AOSD and AITD share molecular mimicry on the IFN-γ and interleukin level.[10] Cross reactivity of other autoantibodies with thyroid antigens or anti-thyroid autoantibodies with others results in concurrent diseases (10). Genetically, HLA-DRB1*04 alleles are correlated in both the diseases (11, 12). So far, only seven reports have been published on the co-existence of AOSD and AITD (**Table.2**). Among them, only two involved hypothyroidism similar to this study's case whereas all of the other studies had hyperthyroidism. At present, it is believed that the two diseases can interact with each other by their shared pathogenesis as there is no clear link between the coexistence of AOSD and AITD.

Table-2: Characteristics of patients with AOSD and AITD.

Authors, (Reference)	Age, year	Gender	Type of AITD	Response to steroids
Chen et al. (8)	50	Female	Basedow's disease	Good
Stagi et al. (13)	37	Female	Grave's disease	Good
Kaltenbach et al. (14)	36	Female	Hypothyroidism	Good
Fang et al. (15)	NA*	NA*	Hyperthyroidism	NA*
Inoue et al. (16)	45	Female	Hyperthyroidism	Good
Hu et al. (17)	43	Female	Grave's disease	Good
Ulas et al. (18)	17	Female	Hypothyroidism	Good

*NA= Details of case report not available in literature, AITD: Autoimmune thyroid disease, AOSD: Adult-onset still's disease.

4- CONCLUSION

The association of AOSD and AITD is rare and an explicit relationship is hard to acquire. They share common pathogenesis and could interact with each other. Screening AITD is recommended, especially in female patients with AOSD.

5- ABBREVIATIONS

AOSD: Adult-onset still's disease,
AITD: Autoimmune thyroid disease,
MCH: Major histocompatibility complex,
IFN-γ: interferon-gamma,
IL: Interleukin,
TNF- α: Tumor necrosis factor- alpha,
HLA: Human leukocyte antigen,
Th: T-Helper cells.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Still GF. On a form of chronic joint disease in children. Archives of disease in childhood. 1941 Sep;16(87):156.

2. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, Kashiwazaki S, Tanimoto K, Matsumoto Y, Ota T. Preliminary criteria for classification of adult Still's disease. The Journal of rheumatology. 1992 Mar 1;19(3):424-30.

3. Huber A, Menconi F, Corathers S, Jacobson EM, Tomer Y. Joint genetic susceptibility to type 1 diabetes and autoimmune thyroiditis: from epidemiology to mechanisms. Endocrine reviews. 2008 Oct 1;29(6):697-725.

4. Tomer Y. Mechanisms of autoimmune thyroid diseases: from genetics to epigenetics. Annual Review of Pathology: Mechanisms of Disease. 2014 Jan 24;9:147-56.

5. Mihailova D, Grigorova R, Vassileva B, Mladenova G, Ivanova N, Lissitchky K, Dimova E. Autoimmune thyroid disorders in juvenile chronic arthritis and systemic lupus erythematosus. InRheumaderm. Springer: Boston; MA. 1999 (pp. 55-60).

6. Van de Putte LB, Wouters JM. Adult-onset Still's disease. Bailliere's clinical rheumatology. 1991 Aug 1;5(2):263-75.

7. Terkeltaub R, Esdaile JM, Décary F, Harth M, Lister J, Lapointe N. HLA—Bw35 and Prognosis in Adult Still's Disease. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1981 Dec;24(12):1469-72.

8. Chen DY, Lan JL, Lin FJ, Hsieh TY, Wen MC. Predominance of Th1 cytokine in peripheral blood and pathological tissues of patients with active untreated adult onset Still's disease. Annals of the Rheumatic Diseases. 2004 Oct 1;63(10):1300-6.

9. Zhao R, Zhou H, Su SB. A critical role for interleukin-1β in the progression of autoimmune diseases. International immunopharmacology. 2013 Nov 1;17(3):658-69.

10. Paul S, Li L, Kalaga R, O'Dell J, Dannenbring RE Jr, Swindells S et al. Characterization of thyroglobulin-directed and polyreactive catalytic antibodies in autoimmune disease. J Immunol. 1997; 159(3):1530-36.

11. Joung CI, Lee HS, Lee SW, Kim CG, Song YH, Jun JB et al. Association between HLA-DR B1 and clinical features of adult onset Still's disease in Korea. Clin Exp Rheumatol. 2003;21(4):489-92.

12. Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset still's Disease. Ann Rheum Dis 2006; 65: 564-72.

13. Stagi S, Giani T, Simonini G, Falcini F. Thyroid function, autoimmune thyroiditis and celiac disease in juvenile idiopathic arthritis. Rheumatology 2005; 44: 517-20.

14. Kaltenbach G, Lujic J, Arpin-Bott MP, Imler M. Adult onset still's disease and subacute thyroiditis. Rev Med Interne 1996; 17(5): 427-31.

15. Hu Y, Wang H, Deng J. Adult-onset Still's disease associated with thyroid dysfunction: case report and review of the literature. The open rheumatology journal. 2014; 8: 9.

16. Inoue R, Kato T, Kim F, Mizushima I, Murata T, Yoshino H et al. A case of adult-onset still's disease (AOSD)-like manifestations abruptly developing during confirmation of a diagnosis of metastatic papillary thyroid carcinoma. Mod Rheumatol. 2012 Sep; 22(5):796-800.

17. Hu Y, Wang H, Deng J. Adult-onset Still's disease associated with thyroid dysfunction: case report and review of the literature. The open rheumatology journal. 2014; 8: 9.

18. Ulas T, Dal MS, Bes C, Borlu F, Buyukhatipoglu H. An adult-onset still's disease with autoimmune thyroiditis. Mymensingh medical journal: MMJ. 2012 Jul 1; 21(3):570-2.