Commentary: ‘Case Report: A Rare Case of Elderly-Onset Adult-Onset Still’s Disease in a Patient With Systemic Lupus Erythematosus’

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Keywords: AOSD, auto-inflammatory disease, myelodysplastic/myeloproliferative disorders, VEXAS syndrome, autoimmunity

A Commentary on

Case Report: A Rare Case of Elderly-Onset Adult-Onset Still’s Disease in a Patient With Systemic Lupus Erythematosus

By Hirooka Y, Okuda S, Sugiyama M, Shiga T, Nozaki Y, Kinoshita K, Funachi M and Matsumura I (2022). Front. Immunol. 13:822169. doi: 10.3389/fimmu.2022.822169

INTRODUCTION

With great interest, we read the recent article entitled ‘Case Report: A Rare Case of Elderly-Onset Adult-Onset Still’s Disease in a Patient With Systemic Lupus Erythematosus’, published online in your journal. In this paper, Hirooka et al. reported the case of an 80-year-old Japanese woman with systemic lupus erythematosus who experienced biological and clinical features compatible with adult-onset Still’s disease (AOSD).

DISCUSSION

We were challenged firstly by the co-occurrence of two rare diseases and secondly by their very late onset. Occurrence of SLE after 75 years of age is a rare condition, this disease being mainly affecting women of reproductive age between the second and fourth decades of life with late onset (>50 years old) in only 5% to 20% (1, 2). In the past, SLE was reported as part of the autoimmune manifestation of myelodysplastic syndrome (3–5). The patient presented ACR EULAR criteria for SLE, but the natural history with an evolution toward an AOSD like presentation makes us wonder if arguments for myelodysplasia were looked for at this stage, particularly clonal haematopoiesis with myeloid NGS.

Beck et al. (6) with their recent description of VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) highlighted the existence of autoinflammatory syndrome of late onset.

Abbreviations: AOSD, adult-onset Still’s disease; UBA1, ubiquitin-like modifier activating enzyme 1; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome.
associated with a somatic mutation in UBA1, a gene encoding ubiquitin-like modifier activating enzyme 1. Its phenotype is still extending but mostly characterized by fever, skin lesions, lung infiltrates, arthralgia, lymph node, and biological inflammatory syndrome with haematological abnormalities including macrocytic anaemia and myelodysplastic syndrome (7). In 2022, VEXAS is considered as a differential diagnosis for AOSD particularly in the elderly (8) and previous diagnosis of AOSD have been rectified a posteriori with UBA1 screening (9).

In addition to the late onset of AOSD and the existence of autoimmunity, cutaneous signs appeared atypical. The authors rightly noticed the works of Maruyama et al. and Mollaeian et al. (10, 11) about atypical skin rash reported in early-onset AOSD, but these patients did not benefit from screening for VEXAS either. Moreover, the oedema described on both eyelids in the case reported reminds us of the 10 patients with periorbital oedema over the 116 VEXAS syndromes from the French cohort but also the 4 patients identified as undifferentiated systemic autoinflammatory disorder in our recent work (8, 12).

Therefore, we think it would be useful to know the red blood cell mean corpuscular volume to consider macrocytosis or not but also more intel about the bone marrow, especially the presence or absence of vacuoles in myeloid progenitors. Bone marrow showed no finding of malignant disease, but has exploration for clonal haematopoiess been done with myeloid NGS? If not, it would be a true asset for diagnosis exploration as far as screening for UBA1 mutation in Sanger technique is concerned.

Finally, we have of course noticed that the patient was a woman, making the probability diagnosis for VEXAS syndrome, an X-linked disease, low but with a few cases reported in women (7, 13) thanks to X monosomy, skewed X inactivation, uniparental disomy or biallelic mutation. Female chromosome X mosaicism is age-related and preferentially affects the inactivated X chromosome. This patient could also have one of the ‘VEXAS-like diseases’, with late-onset autoinflammatory disease, part of the actual USAID, secondary to a clonal haematopoiess whose mutation we are going to identify in the future.

**AUTHOR CONTRIBUTIONS**

DM wrote the manuscript. All authors contributed to the article and approved the submitted version.

**REFERENCES**

1. Riveros Frutos A, Holgado S, Sanvisens Bergé A, Casas I, Olivé A, López-Longo FJ, et al. Late-Onset Versus Early-Onset Systemic Lupus: Characteristics and Outcome in a National Multicentre Register (RELESSER). *Rheumatol Oxf Engl* (2021) 60(4):1793803. doi: 10.1093/rheumatology/keaa477

2. Medlin JL, Hansen KE, Fritz SR, Bartels CM. A Systematic Review and Meta-Analysis of Cutaneous Manifestations in Late- Versus Early-Onset Systemic Lupus Erythematosus. *Semin Arthritis Rheum* (2016) 45(6):6917. doi: 10.1016/j.semarthrit.2016.01.004

3. Bouali F, Berrah A, Si Ahmed-Bouali D, Harrieche F, Benhalima M, Hamladji RM, et al. Immunological Abnormalities in Myelodysplastic Syndromes. Prospective Study (Series of 40 Patients). *Rev Med Interne* (2005) 26(10):77783. doi: 10.1016/j.revmed.2005.06.012

4. Mekinian A, Grignano E, Braun T, Decaux O, Liozon E, Costedoat-Chalumeau N, et al. Systemic Inflammatory and Autoimmune Manifestations Associated With Myelodysplastic Syndromes and Chronic Myelomonocytic Leukaemia: A French Multicentre Retrospective Study. *Rheumatol Oxf Engl* (2016) 55(2):291300. doi: 10.1093/rheumatology/kev294

5. Dalamaga M, Karmaniolas K, Matekovits A, Migdalis I, Papadavid E. Cutaneous manifestations in Relation to Immunologic Parameters in a Cohort of Primary Myelodysplastic Syndrome Patients. *J Eur Acad Dermatol Venereol* JEDV (2008) 22(5):5438. doi: 10.1111/j.1468-3083.2007.02520.x

6. Beck DR, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic Mutations in UBA1 and Severe Adulthood Autoinflammatory Disease. *N Engl J Med* (2020) 383(27):262838. doi: 10.1056/NEJMoa2026834

7. Georgin-Lavialle S, Terrier B, Guedon AF, Hebbig M, Comont T, Lazaro E, et al. Further Characterization of Clinical and Laboratory Features Occurring in VEXAS Syndrome in a Large-Scale Analysis of Multicenter Case-Series of 116 French Patients. *Br J Dermatol* (2021) 186(3):564–74. doi: 10.1111/bjd.20805

8. Delplanque M, Aouba A, Hirsch P, Fenaux P, Graveleau J, Malard F, et al. USAID Associated With Myeloid Neoplasms and VEXAS Syndrome: Two Differential Diagnoses of Suspected Adult Onset Still’s Disease in Elderly Patients. *J Clin Med* (2021) 10(23):5586. doi: 10.3390/jcm10235586

9. van der Made CI, Potjewijd J, Hoogstiens A, Willems HPJ, Kwakernaak AI, de Sevaux RGL, et al. Adult-Onset Autoinflammation Caused by Somatic Mutations in UBA1: A Dutch Case Series of Patients With VEXAS. *J Allergy Clin Immunol* (2021) 149(1):432–39.e4. doi: 10.1016/j.jaci.2021.05.014

10. Maruyama A, Kokuzawa Y, Yamauchi Y, Kirino Y, Nagai H, Inoue Y, et al. Clinical Features of Elderly-Onset Adult-Onset Still’s Disease. *Mod Rheumatol* (2020) 31(4):862–8. doi: 10.1080/14397595.2020.1829430

11. Mollaeian A, Chen J, Chan NN, Nizialek GA, Haas CJ. Adult Onset Still’s Disease in the Elderly: A Case-Based Literature Review. *BMC Rheumatol* (2021) 5(1):12. doi: 10.1186/s41927-021-00183-6

12. Papa R, Rusmini M, Volpi S, Caorsi R, Picco P, Grossi A, et al. Next Generation Sequencing Panel in Undifferentiated Autoinflammatory Diseases Identifies Patients With Colchicine-Responder Recurrent Fevers. *Rheumatol Oxf Engl* (2020) 59(2):34460. doi: 10.1093/rheumatology/kez270

13. Barba T, Jamilouy X, Durel C-A, Bourbon E, Mestrallet F, Suobert P, et al. VEXAS Syndrome in a Woman. *Rheumatol Oxf Engl* (2021) 60(11):4023. doi: 10.1093/rheumatology/keab392

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