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Adult onset Still's disease associated with malignancy—Cause or coincidence?

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ABSTRACT

Objective: To analyze all patients with adult onset Still's disease (AOSD) and malignancy described in the literature and to discuss their relation to each other.
Method: Demographic, clinical, and laboratory characteristics of one index patient with AOSD seen in our institution who subsequently developed a malignant disease were compared with all other cases of AOSD and malignancy identified by a PubMed literature research. Furthermore, characteristics of AOSD patients with malignancy were compared to those without malignancy.
Results: We found 46 articles in English, French, Japanese, Korean, and Spanish language reporting 47 cases in addition to our own case. In 36 patients, the diagnosis of AOSD could be confirmed by retrospectively applying classification criteria according to Yamaguchi, Fautrel, and Crispin. The median time between diagnosis of AOSD and subsequent detection of a malignant disease was 9 months, 50% had a hematological disorder and 50% a solid tumor. In 33%, the symptoms of AOSD resolved after successful therapy of the neoplastic disease. Red flags for paraneoplastic AOSD were onset of symptoms at higher age, atypical features of rash, highly elevated lactate dehydrogenase, atypical cells in the differential blood count, and high concentrations of the soluble interleukin-2 receptor.
Conclusion: A disease resembling AOSD can precede the clinical appearance of a hematologic malignancy or a solid tumor. Thorough diagnostic work-up of AOSD to rule out malignancy and awareness to conspicuous signs for malignancy-associated AOSD are therefore essential in the clinical work-up of such patients.

Adult onset Still's disease (AOSD) is a rare disease [1–3], initially described by Bywaters in 1971 [4]. It is characterized by an evanescent, salmon-colored rash, which is macular or maculopapular, and appears usually simultaneously with high fever, another criterion for AOSD. The fever mostly occurs in a quotidian or double-quotidian pattern [5]. Most patients also present with arthritis and leukocytosis. Other symptoms, like lymphadenopathy, splenomegaly, sore throat, pleuritis, pneumonitis, or pericarditis, are also frequent [6].

Different sets of classification criteria have been published for AOSD. They share the requirement to exclude infectious, malignant, or autoimmune diseases [7–9]. Therefore, in case a malignant process unmasks in a patient, who had been diagnosed with AOSD, various categories of relationship are possible: This could represent (1) a true paraneoplasia, (2) a misinterpretation of tumor symptoms for AOSD, (3) mere coincidence, or (4) a monoclonal malignant proliferation of immune cells due to strong, initially polyclonal autoimmune proliferation, or during immunosuppressive therapy. Prompted by one case in our own clinic, we performed a systematic literature search to analyze all patients with a combination of AOSD and malignancy described up to now, to gain better insight into the relation between AOSD and malignancy.

Materials and methods

A systematic literature research in PubMed for the years 1971–2015 using the search terms "adult onset Still's AND paraneopl*," "aosd AND paraneopl*," "malign* AND adult onset still's," "malign*

Abbreviations: ALAT, alanine aminotransferase; ANA, antinuclear antibodies; AOSD, adult onset Still's disease; ASAT, asparatate aminotransferase; CRP, C-reactive protein; DMARD, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IL, interleukin; LDH, lactate dehydrogenase; maAOSD, malignancy-associated AOSD; n, number; NSAID, nonsteroidal anti-inflammatory drug; PET-CT, ^{18}F-fluoro-deoxy-glucose positron emission tomography in combination with computed tomography; Q_1, first quartile; Q_3, third quartile; RF, rheumatoid factor; sIL-2R, soluble IL-2 receptor.

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AND aosd," "cancer AND aosd," and "cancer AND adult onset still's" retrieved 167 articles. All of them were screened in full-text version and 34 of them were included. Additional references quoted in these articles were checked, which led to the inclusion of 12 additional full-text articles. We included all cases with malignancies, in which a diagnosis of AOSD was made or was considered likely at least temporarily by the authors.

The case reports were reviewed in full length in original language and analyzed for clinical and laboratory features of AOSD according to classification criteria of Yamaguchi, Fautrel, and Crispin. It should be emphasized that application of the Yamaguchi-criteria specifically asks for exclusion of any malignant disease. This requirement was set aside for the purpose of this analysis. A prerequisite for the use of the Crispin-criteria is an in-patient work-up for fever of unknown origin for at least 1 week. For this analysis, we assumed that this was the case, although it was not explicitly mentioned in every manuscript. A problem with the use of the Fautrel-criteria is the fact that one of their six major criteria is the detection of a low level of glycosylated serum ferritin. This parameter was not reported in most of the published manuscripts, therefore this criterion was counted as "not fulfilled" in those cases.

Using these criteria, the established or presumptive diagnosis of AOSD was checked and confirmed or rejected in each individual case. In those confirmed cases, patient demographics as well as type and stage of the underlying malignancy and the lag time of its diagnosis after the first inflammatory symptoms were analyzed. Finally, we examined how cancer therapy influenced the course and outcome of AOSD manifestations.

Results

Index patient

A 61-year-old man developed increasing myalgia and arthralgia, remitting fever up to 39°C and shivering for 1 week. He had already received treatment with NSAIDs and oral prednisone by his general practitioner. In addition, he had arrhythmia of atrial fibrillation and chronic sinusitis at the time of his initial presentation in our clinic. A prostate cancer had been removed 6 years earlier and follow-up examinations had shown no signs for recurrence or metastases.

Physical examination demonstrated arthralgia and myalgia without synovitis in the shoulders, knee joints, right foot, and the left thigh. No lymphadenopathy, splenomegaly, or sore throat could be detected. Ultrasound examination revealed small bilateral pleural effusions but no hepatosplenomegaly or lymphadenopathy. During his work-up, he developed maculopapular exanthema of his trunk, which did not parallel fever flares.

His laboratory tests showed a white blood cell count of 16.8 × 10^3/μl with 93% neutrophils and no pathologic cells in the differential count. CRP (181.3 mg/l) and LDH (360 U/l) were elevated, transaminases in normal range. Antinuclear antibodies were borderline with a titer of 1:100 and rheumatoid factor was negative. There was an elevation of serum levels of ferritin (699 ng/ml), IL-18 (2160 pg/ml), and soluble IL-2 receptors (3363 U/ml).

Because the rash was not entirely typical and did not parallel fever flares and because the ANA titer was not completely negative, in this case Fautrel but not Yamaguchi or Crispin classification criteria were fulfilled. A presumptive diagnosis of AOSD was made and treatment with anakinra in addition to 20 mg prednisone was started. This regimen led to partial remission, fever and rash subsided. A therapy with 20 mg/wk methotrexate was started and steroid dose was tapered. Seven months after start of his initial symptoms, the patient again developed pyrexia and a worsening of his general condition. His platelet count dropped to 74 × 10^3/μl and within the next few days atypical, large lymphocytes appeared in his peripheral blood. A bone marrow biopsy was performed and the diagnosis of high-grade malignant B-cell lymphoma of Burkitt type with leukemic spreading was established. The patient received combination chemotherapy according to the German acute lymphatic leukemia protocol (GMALL) [10] and achieved complete hematological remission and all AOSD-like symptoms disappeared. Two years later, the patient is still in complete remission with 2.5 mg of prednisone and free of symptoms.

Literature review

Clinical manifestations and demographics

We were able to identify 46 publications with 48 patients in the literature [11–56] (including our own case), in which the patients were given a definite diagnosis of AOSD or in which AOSD was discussed as a differential diagnosis by the authors and a simultaneous or subsequent detection of a malignant disease was described.

When the diagnosis of AOSD was evaluated retrospectively using the criteria of Yamaguchi, Fautrel, and Crispin, 36 patients fulfilled at least one of these sets of criteria and therefore are considered malignancy-associated AOSD (maAOSD) throughout this article. This article analyses demographic, clinical, and laboratory characteristics of those 36 maAOSD patients including our own patient described above.

A total of 34 cases fulfilled the criteria of Yamaguchi, 29 of those also the criteria of Fautrel and 21 those of Crispin. A total of 21 could be classified as AOSD, retrospectively by all three sets of criteria. As discussed above, our own patient only fulfilled the criteria of Fautrel and one additional patient only those of Crispin [15]. In eight cases the patients did not fulfill any of the three sets of classification criteria [13,14,17,19,21,23,36,42] and in four the data given were not sufficient to re-evaluate the diagnosis of AOSD [12,46,55,56].

In 72% of all cases AOSD symptoms preceded the tumor diagnosis by a median of 9 months (first quartile (Q_1) 0 months and third quartile (Q_3) 13 months). In eight patients, the onset of AOSD symptoms and the detection of a neoplasm occurred simultaneously, and only in two they appeared after the detection of a malignancy or during its treatment [24,51] (Fig.). The mean age of the patients at the onset of the symptoms of maAOSD was 50 ± 15 years. In total, 21 male and 15 female patients were identified.

All patients except of one [43] presented with fever, 50% with arthralgia and 44% with arthritis. In total, 75% had a typical rash, but there were also three patients with atypical features of their

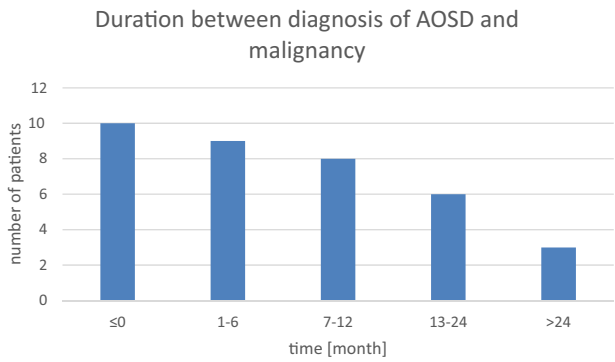

Fig. Distribution of time lag between onset of AOSD symptoms and detection of malignancy.