Clinical Spectrum of Adult-Onset Still's Disease in Patients Presenting At A Tertiary Care Hospital in Pakistan: A 16-Year Follow-Up Study

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Research Article

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Abstract

Objectives

Adult-onset Still's Disease (AOSD) is a rare systemic auto-inflammatory disorder with a low incidence rate and limited data. This study aims to lay down the clinical and laboratory spectrum, associated complications, and outcomes of patients who presented to a tertiary care center – in order to identify any regional variation in the presentation and enable physicians to develop a thought process in patients without characteristic features.

Materials and Methods

We reviewed the records of patients from January 2005 - February 2021 who presented with symptoms consistent with AOSD, using the Yamaguchi criteria. The patients' clinical symptoms, laboratory values, therapeutic management, complications, and outcomes were analysed. Descriptive statistics were produced to illustrate the pattern of the disease.

Results

The mean age of patients was 37.7 years, with a male to female ratio of 1:1. Fever and arthralgia was seen in 90%, a salmon-coloured rash in 60%, and leukocytosis in 80%. 30% presented with a sore throat and recent lymphadenopathy, 40% with hepatomegaly and/or splenomegaly on imaging, 100% with abnormal liver function tests. Steroids were used as first-line treatment. Most patients did not present with common, previously reported, complications of AOSD.

Conclusions

The clinical aspects in this study are, to a large part, comparable to those seen in other parts of the world. Thus, a comprehensive analysis of AOSD would enable physicians to broaden their minds and keep it as a top differential in atypical presentations – enhancing patient care by preventing a delay in diagnosis and initiation of prompt management.

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic auto-inflammatory disorder characterized by the Yamaguchi criteria - migratory inflammatory arthritis, quotidian fevers, leukocytosis and a salmon-coloured maculopapular rash.(1) Epidemiological studies on AOSD are limited due to its scarcity – the estimated annual incidence is 0.16, 0.22, 0.4 and 0.62 per 100,000 in France, Japan, Norway, and Turkey, respectively.(1) This study aims to lay down the clinical spectrum of AOSD to identify any regional

variation in the presentation and enable physicians to develop a thought process in patients without characteristic features.

The pathophysiology of AOSD has been attributed to the role of macrophage cell activation, which leads to T-helper 1 (Th1) cell cytokine activation. Furthermore, pro-inflammatory cytokines such as interleukin – 1, -6, and – 18 have also been proposed to play a role. (2)

AOSD is not usually fatal. Its mortality is primarily associated with life-threatening complications that can ensue such as macrophage activation syndrome (MAS) and disseminated intravascular coagulation (DIC) with a mortality of 15.7% and 16% respectively. (3) Other complications include fulminant hepatitis, cardiac or pulmonary complications, hemophagocytic lymphohistiocytosis and amyloid A amyloidosis. (3)

There is no gold standard laboratory or imaging test available for diagnosing AOSD. There are non-specific lab parameters such as serum ferritin, AST, and ALT that have shown to be raised, however, it is largely a diagnosis of exclusion. (4) In addition, a recent case report on an Asian woman portrayed the measurement of Interleukin-18 as a good diagnostic biomarker to monitor disease activity. (5)

Materials And Methods

This article does not contain any studies with human participants performed by any of the authors. After obtaining ethical approval from the Ethical Review Committee (ERC), data review of the last 16 years was performed at a tertiary care centre from January 2005 to February 2021 for patients diagnosed with AOSD – 10 patients were selected to be included in this retrospective descriptive study. Patients who were already diagnosed with AOSD prior to presenting at this centre were excluded from this study, as well as patients presenting with an uncertain disease that resembled AOSD. In addition, Yamaguchi exclusion criteria was applied to omit individuals diagnosed with infections, malignancies (such as malignant lymphoma), and other rheumatic diseases (like systemic vasculatures).

This study viewed information from patient files only. Identification of the study participants was kept strictly confidential between the primary investigators. The case files were analysed for demographic data (including age, gender, and comorbid), clinical and laboratory findings that supported Yamaguchi criteria, therapeutic management, complications, and outcomes. Data was recorded on a standard excel sheet, and statistical analysis was performed via Statistical Package of Social Sciences (SPSS) version 22. Categorical variables were compared using chi-squared test.

Results

Amongst the 10 patients in this study, the mean age was 37.7 years with a range of 26–77. Moreover, males and females were equally distributed.

Frequencies of symptoms that satisfied Yamaguchi's major and minor criteria amongst the patients that presented with AOSD are illustrated in Fig. 1. Within the research sample, 5 patients presented with all 4 of the major criteria, and 4 presented with 3 out of 4 major criteria.

At the time of presentation, high spiking fever (> 39°C) was seen in 90% of them for a duration greater than 2 weeks. Arthralgia with pain lasting greater than 2 weeks was described by 90% of the patients. The classic salmon-pink maculopapular rash was noted in 60% of the patients. Moreover, 30% of the patients had a history of sore throat and lymphadenopathy before admission. 40% of the patients showed imaging evidence of hepatomegaly and/or splenomegaly. Of these, 10% of the patient presented with splenomegaly accompanied with hepatomegaly, and 30% presented with only splenic enlargement.

Leukocytosis was measured as a WBC count > 10,000/ mm^3 alongside > 80% polymorphonuclear cells. 80% of the patients met both criteria. All patients had an elevated serum ferritin. For males, the mean ferritin levels were elevated 7507 above the baseline range, while it was 13,468.28 above the normal range for females. Furthermore, erythrocyte sedimentation rate (ESR) was also elevated in all patients, with a mean level of 93.2 mm/hr and a range of 53–135. Deranged Liver Function Tests (LFT) were present in 90% of the patients - SGPT, GGT, SGOT, total bilirubin (TB), direct bilirubin (DB), and albumin levels were observed. No patient had elevated Albumin levels twice the upper range. Only 10% of the patients had all remaining markers diagnostically elevated at greater than twice the upper range, and 30% of the patients showed no diagnostic elevations in any of the markers. 30% of patients with abnormal LFTS only had isolated elevations in GGT while 10% had both elevated GGT and elevated DB. 20% had isolated elevation of DB.

Of the 10 patients, all males survived while 20% mortality was seen amongst females. Furthermore, no mortality was seen in the age group 20–50 (80% of the total sample) and the only mortality was reported in the age group of 50–80 (20% of the total sample).

40% of the patients had a length of stay in the hospital between 0 to 5 days, 50% between 5 to 10 days, and 10% of the patients were managed in an outpatient setting.

Steroids were used as first-line treatment, with prednisolone as the drug of choice to manage. No patient was managed with biological agents. Dual therapy with azathioprine was used in 20% of the patients, sulfasalazine in 10% of the patients, and methotrexate in 10% of the patients. 20% of the patients were on triple therapy, 10% consisting of prednisolone with azathioprine and methotrexate, and 10% with prednisolone with methotrexate and hydroxychloroquine.

In this study, MAS and DIC were not reported amongst any of the patients. However, a 27-year-old patient had a history of severe pulmonary arterial hypertension with cor pulmonale.

Table 1 summarizes the main clinical features of AOSD from this case series and compares them with those from other studies.

Table 1
(Original). Comparison of laboratory findings of AOSD from different studies

	This Study (8)	Baxevanos[10] (22)	Chen[11] (61)	Kong[12] (104)	Pouchot[13] (62)	Sfriso[14] (245)	Singh[15] (14)
Region	Pakistan	Greece	China	China	Canada	Italy	India
M:F (F%)	3:5 (62.5)	15:7 (31.8)	29:32 (52.5)	26:78 (75)	34:28 (45.2)	129:116 (47.3)	9:5 (37.5)
Mean Age (years)	37.6	32	30.11 ± 10.75	16–64	Median = 24	38.8	29.85
Fever	100	100	100	100	100	92.6	100
arthralgia	100	91	80.33	90	100	93	100
Rash	62.5	73	78.69	95	87.1	67.7	57.1
Leukocytosis	75	91	80.33	98	93.5	81	-
Sore throat	37.5	73	83.61	78	91.9	62	35.7
Lymph-adenopathy	37.5	73	52.46	66	74.2	60.4	71.4
Hepato-splenomegaly	50	-	63.93	57	54.8	41.7	57.1
Abnormal LFTS	87.5	86	60.66	-	80	53.5	50
Negative ANA/RF	37.5	95	90	-	89	-	100
Elevated Serum Ferritin	100	95	94	99	-	56.4	50
Elevated ESR	100	95	98.36	96	100	-	100

Discussion

The diagnosis of AOSD is currently reliant on a cluster of nonspecific clinical symptoms, thus the lack of specific tests for AOSD makes it an enigmatic diagnosis of exclusion, with numerous differentials, leading to a big discrepancy between the initial presentation and establishment of a definitive diagnosis. (12)

Within this study, the calculated incidence rate of AOSD was 0.625 cases per year. However, this is moderately lower than those calculated by other epidemiological studies. (1) The disparity in the results may be due to the exclusion of those patients who were diagnosed prior to presenting at the hospital. It is noteworthy to mention that even though this tertiary care centre receives cases from all over the country, many cases are referred from places close to the localities of the people where they presented first.

Our cases presented in the range of ages 26–77 years, with one patient diagnosed at age 70. This is consistent with previous studies where AOSD has been cited as a disease mainly affecting younger adults, with a rare occurrence in individuals over the age 60 years.(13) Moreover, the mean age of the patients in this study was 37.7 years, which was similar to that of a study conducted in Italy in which the mean reported was 38.8.(10) However, literature from Canada and India presented a mean age of mid-to-late 20s,(9, 11) while other studies recorded a mean in the early 30s.(6, 8) Furthermore, AOSD has been observed to show a bimodal age distribution of 15–25 and 36–46 years of age.(14) It is possible that the mean of the data in this study became skewed because of an outlier - one patient was diagnosed at 77 years, shifting the mean to the right.

Although AOSD is more prevalent in females, (8) existing literature also portrays male preponderance. (6, 11) Our cases exhibited an equal distribution amongst males and females and this was also supported by prior studies showing no sex predisposition.(7, 9, 10) Where we suspect autoimmune diseases more in females due to their predisposition, we should also have a high degree of suspicion in males with a compatible presentation.

Fever, arthralgia, neutrophilic leukocytosis and abnormal LFTs were the most common findings amongst our patients and similar conclusions were drawn by other studies.(6–11) Furthermore, elevated ESR and hyperferritinemia were comparable to all other studies.(6–11) Hepatosplenomegaly was observed in 40% of the patients who presented with AOSD and this was paralleled by other studies also having a low to moderate occurrence of hepatosplenomegaly via physical examination, ultrasound or other imaging techniques.(7–10) We therefore see that the clinical, laboratory and radiological findings observed in our study are similar to the ones in other epidemiological studies.

The characteristic salmon-coloured rash was seen in 60% of our patients and similar results (57%) were portrayed by a study on AOSD from India. (11) However, studies from other regions like China, Italy, and Greece, showed a higher proportion. (7–10) The discrepancy in data between Southeast-Asian regions and others can be accounted for by the darker skin colour making it difficult to identify a mild rash.

Sore throat and lymphadenopathy at the time of presentation were noted in 30% of our cases and this was paralleled by another study with similar findings.(11) In contrast, multiple studies observed sore throats in over 50% of the cases,(10–14) and a few had near 80% or above.(7–9). Similarly, higher frequencies (> 50%) of lymphadenopathy were observed in the majority in other studies.(6, 8–11) The low proportion of sore throat in our study may be explained by its early onset in the disease process and possible delay in diagnosis of AOSD, resulting in patients not recalling it along with the other

manifestations. With regards to lymphadenopathy, variation may be explained by the dynamic lymph node changes during the disease process.

Pharmacological management of AOSD is centered around glucocorticoids, NSAIDs, and disease-modifying anti-rheumatic drugs (DMARDs).(15) The use of corticosteroids is considered the first-line therapy when systemic symptoms predominate – a recent study concluded that the use of high dose corticosteroids was more effective in inducing remission than the use of low dose corticosteroids. Prednisolone was used as a first-line agent for our patients.

Disease modifying anti-rheumatic drugs (DMARDs) and biologic agents constitute second-line therapies in case corticosteroids fail to initiate a clinical response. (16) According to a case report, once a day administration of IL-1 receptor antagonist Anakinra led to the reduction of the dose of corticosteroids – which was useful in controlling the side effects of corticosteroids such as the decompensation of Diabetes Mellitus. However, due to the hefty cost, it is not commonly used, (17) and it was not used in our patients either. Therefore, wherever possible, tapering off steroids and switching to such alternatives can ensure better treatment compliance and prevent glucocorticoid related side effects.

MAS has been reported as the most severe complication of AOSD, seen in 10% with a mortality of 15.7% in one study, and an incidence of 15% with a high mortality rate between 10–41% in another.(3, 18) None of our patients were diagnosed with MAS likely due to the limited number of cases and the rarity of this complication. Interestingly, a lesser common complication associated with AOSD is pulmonary hypertension, (18) which was noted in 1 patient that presented with severe pulmonary arterial hypertension and associated cor pulmonale.

The only mortality reported in this study was of a 77-year old man. However, sufficient evidence is not present to support AOSD-related complications as the cause of death in this patient. One study reported the mean age of patients who died in hospitals as 62.4 years ± 3.1 and concluded that the older age and associated comorbidities were a predictive factor for the higher incidence of mortality in patients with AOSD.(19) Early identification of AOSD in an older patient therefore is more crucial.

This study highlights specific strengths as observed by the data and its interpretation. It assisted in the thorough analysis of AOSD symptoms and explored the Yamaguchi criteria extensively amongst all patients. Additionally, many of the frequencies observed in this study were comparable to those of other studies as well.

This study posed certain limitations. It was conducted in a single-center tertiary care hospital, and despite patients coming from all over the country, the patient sample's epidemiological data is not reflective of the country's population. Thus, limitations of this study should be considered alongside its findings.

Conclusion

The diagnostic difficulty and delay due to the rarity of AOSD, and lack of specific diagnostic biomarkers, can lead to recurrent acute flare ups, inappropriate therapy, and severe complications, because of both the disease and the incorrect management. Understanding the variations in clinical presentations, and the unfavourable complications is crucial to the management of AOSD. Clinical aspects of AOSD in this study are, to a large part, comparable to those seen in other parts of the world. Thus, this study has comprehensively analysed the clinical spectrum of AOSD and hopes to develop an enhanced thinking process within the global medical community. This will enable physicians to broaden their minds and be more vigilant – keeping AOSD as a top differential in atypical presentations. We would therefore witness a huge impact on patient care – by preventing a delay in diagnosis, and the initiation of prompt management. We therefore hope this study becomes a platform for physicians and researchers to think about refining the guidelines and making a move towards identifying more specific lab parameters.

Declarations

Ethical Statement:

The authors consciously assure that for the manuscript above, the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.

2) The paper is not currently being considered for publication elsewhere.

3) The paper reflects the authors' own research and analysis in a truthful and complete manner.

4) The paper properly credits the meaningful contributions of co-authors and co-researchers.

5) The results are appropriately placed in the context of prior and existing research.

6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.

7) All authors have been personally and actively involved in substantial work leading to the paper and will take public responsibility for its content.

Ethical Approval:

We confirm that the protocol of the research has been approved by the Ethics Review Committee of the institution within which the work was undertaken, and it is in accordance with the relevant guidelines and regulations laid down by the Declaration of Helsinki.

This article does not contain any studies with human participants performed by any of the authors. Approval was taken from the Ethics Review Committee (ERC) prior to the study and was performed according to the standards laid out.

Name: Ethical Review Committee (ERC)

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Consent for Publication:

Not applicable.

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All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing Interest:

The authors declare that they have no competing interests

Conflict of Interest:

The authors declare they have no conflict of interest.

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Author Contribution:

#M.R.: Study design and concept, questionnaire design, expert review of manuscript.

#A.A.: Study design and concept, questionnaire design, expert review of manuscript

S.M.B.: Study design and concept, data collection, data analysis, manuscript writing and review

I.A.: Study design and concept, data collection, manuscript writing.

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Figures

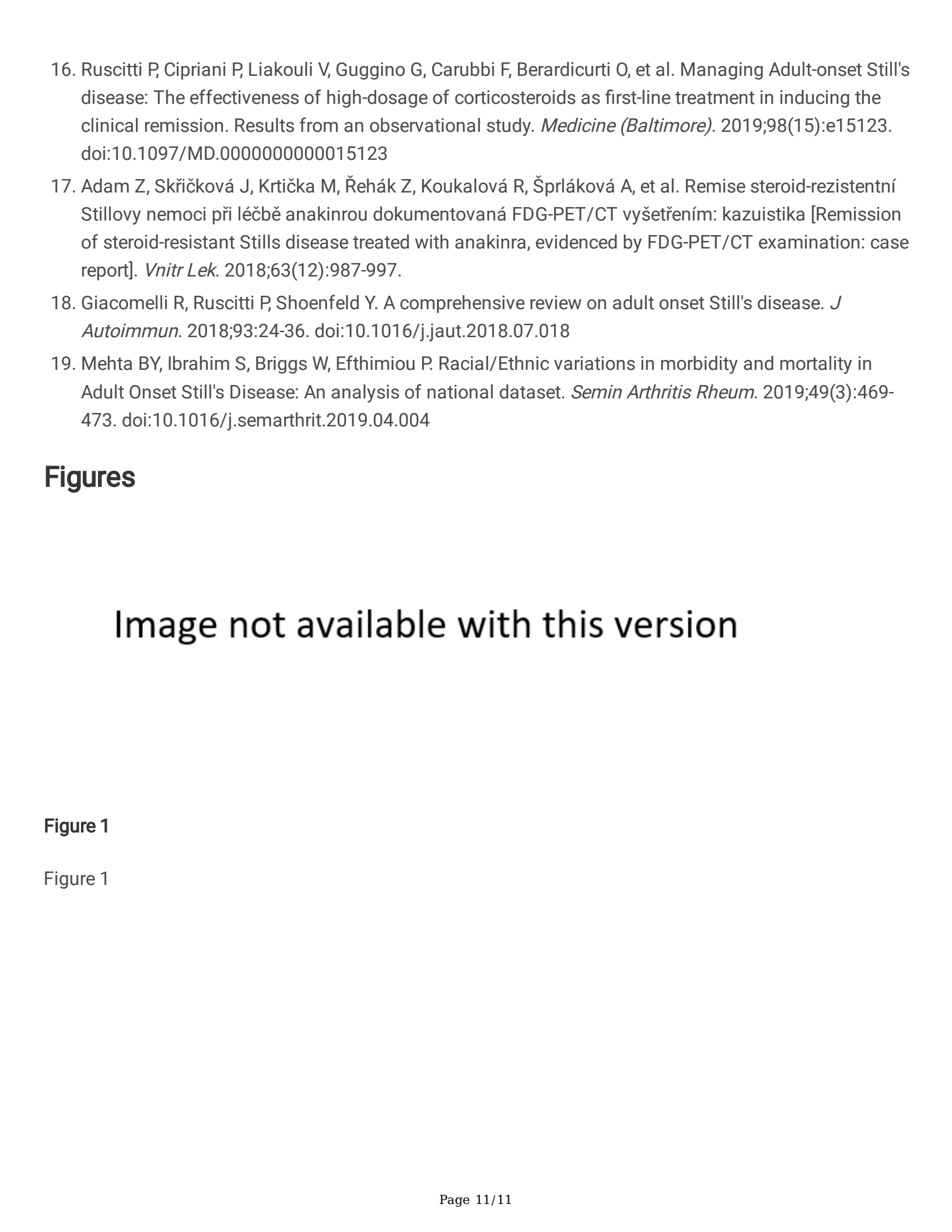

Figure 1

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