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Research Article

LEVELS OF TUMOR MARKERS IN PATIENTS WITH ADULT ONSET STILL DISEASE, AND POSSIBLE RELATIONSHIPS WITH CLINICAL PRESENTATIONS AND OTHER INFLAMMATORY MARKERS

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A B S T R A C T

Background: Adult onset Still Disease (AoSD) is a rare systemic polygenic non-familial autoinflammatory disease. There is no specific biological parameter for diagnosis of AoSD today. The current study was designed to investigate serum level of tumor markers, and possible relationships with clinical presentations and other inflammatory markers in patients with AoSD. It appears that this is the first paper on the association between AoSD and tumor markers.

Methods: A total of 61 patients diagnosed with AoSD were included in this retrospective study. The clinical characteristics and baseline laboratory results at diagnosis were obtained from medical charts. Patients with higher or normal tumor marker levels were subgrouped and compared according to all of the clinical and laboratory parameters. Statistical analysis was performed using Jamovi (Version 1.2.22) and JASP Team (2018). JASP (Version 0.12.2) software. A p-value below 0.05 was accepted as statistically significant.

Results: Data regarding tumor markers was available only for 25 patients (40.9%). Levels of tumor markers (prostate specific antigen in men, cancer antigen 125 in women) were higher than normal in 9 patients (36%). When we compared patients with and without higher than normal tumor markers, the mean age and gender distribution were comparable. In addition, there was no significant difference between the groups in terms of presentation symptoms and laboratory values.

Conclusion: Elevated level of tumor markers is not always an indication of malignancy and also may be detected in AoSD patients. The higher values may be related to inflammation.

INTRODUCTION

Adult onset Still Disease (AoSD) is a rare systemic polygenic non-familial autoinflammatory disease that was defined by Eric Bywaters in 1970 **[1].** It's prevalence in Turkey (6.77/100.000) has been reported to be higher than its worldwide prevalence **[2].** Although the Yamaguchi criteria are the most widely used classification criteria, AoSD is still a diagnosis of exclusion, especially exclusion of infection, other rheumatic diseases and malignancy **[3].**

Serum tumor markers are heterogeneous molecules with elevated concentrations in patients with solid tumors. Although increased serum concentrations are obtained via cell necrosis, changed expression or secretion of different molecules, they can also be found at measurable levels in plasma of healthy individuals under physiologic and/or inflammatory conditions **[4].**

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There are several serum tumor markers that are used for diagnosing and monitoring cancer patients in routine clinical practice.

Although many serum biomarkers have been studied as predictors of disease activity and/or for diagnosis, there is no specific biological parameter for diagnosis of AoSD today. Ferritin is one of the best known markers. Many cytokines including interleukin-1beta (IL-1β), interleukin-18 (IL-18), tumor necrosis factor (TNF) and interleukin-6 (IL-6) regulate ferritin synthesis through hepcidin synthesis **[5].** Among these proinflammatory cytokines, IL-18 has been shown to be more specific than others in the diagnosis of AoSD **[6].** IL-18 has also been shown to contribute to pathophysiological mechanisms of malignancies including gynecological cancers in men and women**[7].**

We aimed to investigate serum levels of tumor markers that may be associated with higher levels of IL-18 and inflammation in patients with AoSD.

MATERIALS AND METHODS

A total of 61 patients were included in our retrospective study. All of the patients were diagnosed with AoSD from June 2010 to December 2020 in the Department of Rheumatology, Pamukkale University School of Medicine, Denizli, and fullfilled the classification criteria of Yamaguchi.

Exclusion criteria were defined as: having other inflammatory diseases, concurrent malignancy or having insufficiently available clinical data, or refusal to participate in the study. Medical histories, and clinical and laboratory analyses were collected from the hospital data system.

Demographic characteristics (age and gender) and clinical presentations including fever, sore throat, arthralgia and skin erupsions at diagnosis were noted exactly. Fever was defined as temperature ≥ 39°C and other clinical manifestations were noted as present or absent. Baseline laboratory results at the diagnosis of AoSD were screened, including serum ferritin levels(ng/mL), erythrocyte sedimentation rate (mm/h), serum c-reactive protein levels (mg/L), white blood cell and neutrophil counts (K/uL), and levels of serum alanine transferase (IU/L) and alkaline phosphatase (IU/L). Neutrophilia was defined as increased polymorphonuclear neutrophils (PMN) counts ≥ 75%, and hyperferritinemia was defined as ≥ 3-fold more than the upper normal value. Serum erythrocyte sedimentation rate (mm/h), serum c-reactive protein level, white blood cell count, and serum alanine transferase and alkaline phosphatase levels exceeding the upper limits were accepted as positively present.

It was noticed that in some AoSD patients (n=25), tumor markers were analyzed for screening of malignancies in accordance with age and gender, prostate specific antigen for males, and cancer antigen 125 for women. All of the patients in this group presented with fever of unknown origin. It was shown that they had no malignant diseases after further investigation at the follow-up. Ultimately they were diagnosed with AoSD. All of them had favorable courses. The elevated tumor markers returned to normal ranges at the sixth month of treatment for each patient.

Ethics committee approval was obtained for this study.

Statistical analysis

In summarizing the data derived from the study, descriptive statistics are presented as mean ± standard deviation and median, minimum-maximum and interquartile range for continuous variables, depending upon the distribution of the variables. Categorical variables are shown as number and precentage. Normality evaluation of numerical variables was perfomed using Kolmogorov Smirnov test.

In comparison of the groups with and without a high level of the tumor markers, independent samples t-test was used when the numerical variables were normally distributed. When the numerical variables were not normally distributed, Mann Whitney U test was used. To compare the aforementionmed groups in terms of categorical variables, Fisher's Exact Test was used if the expected value was below 5 in 2x2 tables.

Statistical analysis was performed using Jamovi (Version 1.2.22) and JASP Team (2018). JASP (Version 0.12.2) software. A p-value below 0.05 was accepted as statistically significant.

RESULTS

Baseline characteristics and laboratory values

A total of 61 patients (26 males and 35 females) with Adult onset Still Disease were included in the study. The mean age of the study subjects was 41.0 ± 13.8 years. The most common presentation symptoms were fever and arthralgia (96.7% for each). The median serum ferritin value was 1485 [10- 93940] ng/mL in the whole patient group. Over 90% of the patients had serum ferritin values ≥ 3-fold more than the upper normal limit. While the percentage of patients who had leucocytosis was 77%, this value was 91.8% for neutrophilia. The serum alkaline phosphatase value was more often higher than normal compared with the alanine aminotransferase value. In table-1, we presented mean age, sex distribution, presentation symptoms and laboratory values of the entire cohort.

Tumor marker levels

Data regarding tumor markers was available for only 25 patients (40.9%). The levels of tumor markers were higher than normal in 9 patients (36%) (table-1). When we compared patients with and without a higher than normal tumor marker, the mean age and gender distribution were comparable. In addition, there was no significant difference between the groups in terms of presentation symptoms and laboratory values (table-2).

Table 1 Mean age, sex distribution, presentation symptoms and laboratory values of the entire study population

	Mean ± SD / n (%)	Median [Min-Max]	Number of patients with abnormal result (%)
Sex			
Male	26 (42.6)		
Female	35 (57.4)		
Age (years)	41.0 ± 13.8	39.0 [19.0- 73.0]	
Fever	59 (96.7)		
Sore throat	32 (52.5)		
Skin rash	42 (68.9)		
Arthralgia	59 (96.7)		
Tumor markers (available in 25 (40.9%) patients)			
Normal	16 (64)		
High	9 (36)		
Ferritin (ng/mL)	5542 ± 15260	1485 [10- 93940]	55 (90.2)
ESR (mm/h)	78.8 ± 37.3	83.0 [3.0- 150.0]	57 (93.4)
CRP (mg/dL)	113.2 ± 89.7	111.0 [0.3- 300.0]	54 (88.5)
WBC count (x10^3/µL)	15460.2 ± 7296.4	14600.0 [3620.0- 39100.0]	47 (77.0)
Neutrophil count (x10^3/µL)	12755 ± 7082	11900 [2110- 34900]	56 (91.8)
ALT (IU/L)	73.9 ± 177.5	32.0 [9.0- 1390.0]	30 (49.2)
ALP (IU/L)	104.8 ± 55.6	100.0 [19.0- 283.0]	59 (96.7)

ESR: erythrocyte sedimentation ratio, CRP: C-reactive protein, WBC: white blood cell, ALT: alanine aminotranspherase, ALP: alkaline phosphatase.

Table 2 Comparison of mean age, sex distribution, presentation symptoms and laboratory values between the groups with and without higher than normal tumor markers

	Tumor markers		
	Normal (n=16)	**High (n=9)**	**P-value**
Sex (%)			
Male	6 (37.5)	4 (44.4)	0.999*
Female	10 (62.5)	5 (55.6)	
Age	46.2 ± 15.7	55.8 ± 10.2	0.078**
Fever(%)	14 (87.5)	9 (100.0)	0.520*

Sore throat (%)	7 (43.8)	5 (55.6)	0.688*
Skin rash (%)	10 (62.5)	4 (44.4)	0.434*
Arthralgia (%)	15 (93.8)	9 (100.0)	0.999*
NLR	7.8 [4.5- 10.0]	6.8 [3.0- 11.2]	0.887***
PLR	183.0 [147.8- 204.8]	207.0 [95.0- 246.0]	0.843***
MPV (fL)	8.6 [7.9- 9.9]	8.3 [7.8- 8.5]	0.321***
Ferritin (ng/mL)	1415.5 [773.0- 2073.8]	1246.0 [710.0- 3289.0]	0.821***
ESR (mm/h)	76.0 [49.5- 108.8]	101.0 [62.0- 120.0]	0.427***
CRP (mg/dL)	63.0 [24.2- 139.5]	85.0 [19.0- 176.0]	0.799***
WBC count ($x10^3$/µL)	14550.0 [7772.5- 18925.0]	13600.0 [13000.0- 14900.0]	0.887***
Neutrophil count ($x10^3$/µL)	11950.0 [3945.0- 15525.0]	11400.0 [10700.0- 12900.0]	0.955***
ALT (IU/L)	46.5 [27.5- 85.0]	35.0 [14.0- 39.0]	0.269***
ALP (IU/L)	95.0 [63.0- 134.2]	110.0 [75.0- 144.0]	0.651***

*: Fisher's exact test was used. Descriptive statistics were presented as n (%).
**: Independent samples t-test was used. Descriptive statistics were presented as mean ± standart deviation.
***: Mann Whitney U test was used. Descriptive statistics were presented as median [Q1-Q3].
Q1: 1st Quartile, Q3: 3rd Quartile
NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV: mean platelet valume, , ESR: erythrocyte sedimentation ratio, CRP: C-reactive protein, WBC: white blood cell, ALT: alanine aminotranspherase, ALP: alkaline phosphatase

DISCUSSION

The conclusion from our study is that tumor markers may have elevated titers in AoSD patients without malignancies. These higher titers may be associated with intense inflammation. Normal values at the sixth month of treatment support this hypotesis.

Not only malignancies, but many inflammatory/infectious diseases and physiological conditions may cause increased levels of tumor markers. Carcinoembryonic antigen (CEA) is significantly increased in patients with inflammatory bowel diseases **[8].** Increased levels of alpha-fetoprotein (AFP) have been shown under physiological conditions such as in pregnancy **[9].** High alpha-fetoprotein levels may also reflect liver cell regeneration after necrosis of hepatic tissue **[10].** Cancer antigen 125 (CA-125) is a glycoprotein expressed on the surface of both ovarian cancer cells and healthy cells of mesothelial origin. Immunohistochemical staining of normal cervical tissue in healthy women demonstrated the synthesis and the secretion of CA-125 in tall columnar cells of the endocervical epithelium **[11].** Raised levels were found in patients with gynecologic tumors, pelvic inflammatory disease, ascites, tubo-ovarian abscess and in healthy women with pregnancy or normal menstrual cycle due to increased local expression in the area of inflammation **[12].** Cancer-associated antigens such as carbohydrate antigen 19-9 (CA 19-9) were also demonstrated in human milk taken from healthy women to form structural units of a mucus glycoprotein **[13].** In rheumatology, SLE patients have elevated CA-125 levels in accordance with disease manifestations and mesothelial involvement **[14].** Chong Hong Lim, *et al*. investigated the clinical application of tumor markers in the screening for malignancy in patients with myositis and stated that tumor markers are not useful as a screening tool **[15].** This is the first study that detected a relationship between serum tumor markers and AoSD. We found high baseline levels that may be associated with inflammation. Due to the retrospective nature of the study, no analysis of associated proinflammatory cytokines such as IL-1β and IL-18 were performed. The return of tumor markers to normal ranges supported our idea. There was no significant difference between the two groups (normal/high tumor markers) in terms of presentation symptoms and other laboratory parameters. This can be explained by the very low number of patients with high baseline tumor markers.

A few limitations of this study are present. We reviewed the clinical data retrospectively in a single center. Because of the low incidence rate, the sample size was small. We also did not compare the data of AOSD patients with those of healthy controls. No analysis of associated proinflammatory cytokines was done because of the retrospective nature of the study.

CONCLUSIONS

In conclusion serum tumor markers may be at higher titers associated with inflammation in these patients. Further studies in larger populations are required to show a clear association.

What is known about this topic

- Not only malignancies, but many inflammatory/infectious diseases and physiological conditions may cause increased levels of tumor markers.
- Clinical application of tumor markers in the screening for malignancy in rheumatology patients is not useful as a screening tool.

What this study adds

Tumor markers may have elevated titers in AoSD patients without malignancies, and these higher titers may be associated with intense inflammation and proinflammatory cytokines.

Conflicts of Interest

The authors declared that they have no conflicts of interest.

Author contributions

All of the authors read and approved the final version of the manuscript.

Tables

Table 1: mean age, sex distribution, presentation symptoms and laboratory values of the entire study population
Table 2: comparison of mean age, sex distribution, presentation symptoms and laboratory values between the groups with and without higher than normal tumor markers

References

1. Bywaters E G. Still's disease in the adult. Ann Rheum Dis. 1971; 30(2):121-133
2. Balci MA, Pamuk ON, Pamuk GE, Uzundere FK, Donmez S. Epidemiology and outcome of adult-onset Still's disease in Northwestern Thrace region in Turkey. Clin Exp Rheumatol. 2015; 33(6):818-23
3. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, *et al*. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992; 19(3):424-430

4. Amayo AA, Kuria JG. Clinical application of tumour markers: a review. East Afr Med J. 2009; 86(12 Suppl):S76-83
5. Fautrel B, Le Moel G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S, *et al*. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J. Rheumatol. 2001; 28(2):322-329
6. Girard C, Rech J, Brown M, Allali D, Roux-Lombard P, Spertini F. Elevated serum levels of free interleukin-18 in Adult onset Still disease. Rheumatology(Oxford). 2016; 55(12):2237-2247
7. Esmailbeig M, Ghaderi A. Interleukin-18: a regulator of cancer and autoimmune diseases. Eur Cytokine Netw. 2017; 28(4):127-140
8. Turner MD, Kleinman MS, Thayer W. Serum carcinoembryonic antigen (CEA) in patients with chronic inflammatory bowel disease. Digestion. 1973; 9(2):116-23
9. Brettes JP, Tourne C, Gandar R. Radioimmunologic determination of alpha fetoproteins in the maternal serum during pregnancy, labor and post-partum period. J Gynecol Obstet Biol Reprod. 1974; 3(6):843-53
10. Esposito R, Pollavini G, De Lalla F. Serum alpha-fetoprotein in viral hepatitis and its complications. Boll Ist Sieroter Milan. 1976; 55(71):59-64
11. de Bruijin HW, van Beeck Calkoen-Carpay T, Jager S, Duk JM, Aalders JD, Fleuren GJ. The tumor marker CA 125 is a common constituent of normal cervical mucus. Am J Obstet Gynecol. 1986; 154(5):1088-91
12. Suzuki M, Sekiguchi I, Ohwada M, Tamada T, Sakurabayashi I, Kawai T. Clinical evaluation of a cancer antigen CA 125 associated with ovarian cancer. Rinsho Byori. 1985; 33(3):285-8
13. Hanisch FG, Uhlenbruck G, Dienst C, Stottrop M, Hippauf E. Ca 125 and Ca 19-9: two cancer-associated sialylsaccharide antigens on a mucus glycoprotein from human milk. Eur J Biochem. 1985; 149(2):323-30
14. Tuncer S, Basaran A. SLE and CA-125. Gynecologic Oncology. 2006; 100(2):444-445
15. Chong Hong Lim, Chih-Wei Tseng, Ching-Tsai Lin, wen-Nan Huang, Yi-Hsing Chen, Yi-Ming Chen. The Clinical Application of Tumor Markers in the Screening of Malignancies and Interstitial Lung Disease of dermatomyositis/polymyositis Patients: A Retrospective Study. SAGE Open Med. 2018; 6:2050312118781895

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