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Comparative analysis of the concentrations of proinflammatory cytokines and glycosylated ferritin in patients with idiopathic recurrent pericarditis and adult-onset Still's disease

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Idiopathic recurrent pericarditis (IRP) and adult-onset Still's disease (AOSD) are polygenic autoinflammatory diseases, in the pathogenesis of which proinflammatory cytokines from the interleukin-1 superfamily play a central role.

Aim. To compare serum concentrations of proinflammatory cytokines and glycosylated ferritin (GF) in patients with IRP and AOSD during an exacerbation.

Material and methods. The study included 15 patients with AOSD, 15 — IRP. The diagnosis of AOSD was established using the Yamaguchi criteria (1992). IRP was diagnosed in accordance with the 2015 European Society of Cardiology on the diagnosis and management of pericardial diseases. Blood sampling from all patients was carried out during the recurrence period prior to the anti-inflammatory therapy initiation.

The serum levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-18 (IL-18), procalcitonin, total ferritin and GF was assessed. The results obtained were compared with levels of biochemical parameters, high-sensitivity C-reactive protein (CRP), as well as with white blood cell (WBC) and neutrophil counts.

Results. The median age in the AOSD group was 28 years, and the IRP — 55 years. An increase WBC count >$10*10^9$/L was detected in 10 and 9 patients in the AOSD and IRP groups, respectively. The concentration of CRP was increased in all patients and did not differ in the study groups (p=0,836).

The highest values of ferritin and GF levels were found in the AOSD group (1416 ng/ml vs 408 ng/ml, p=0,008) and (12% vs 33,9%, p=0,067), respectively. In both groups, increased concentrations of IL-6 and IL-18 were determined. In the AOSD group, the concentration of IL-18 was higher than in the IRP group (2114 pg/ml vs 161,5 pg/ml, p<0,001). IL-6 concentrations in the study groups did not differ (33,9 pg/ml vs 24,9 pg/ml, p=0,4). IL-1β serum concentration in all subjects corresponded to normal values.

Correlation analysis in the AOSD group revealed a direct relationship between the IL-18 and ferritin concentrations (r_s=0,73, p=0,03).

Conclusion. The study established a similar pattern of changes in inflammatory biomarkers in patients with AOSD and IRI. The most informative marker of inflammation was IL-18.

Keywords: idiopathic recurrent pericarditis, adult-onset Still's disease, interleukin-1β, interleukin-6, interleukin-18, glycosylated ferritin.

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Idiopathic recurrent pericarditis (IRP) and adult Still's disease (AOSD) belong to a group of clinically similar rare polygenic autoinflammatory diseases (AID), united by similar pathogenesis [1]. It is assumed that they are based on dysregulation of innate immunity, leading to activation of NLRP3-inflammosome. The synthesis of interleukin-1 (IL-1) and interleukin-18 (IL-18) plays a central role. Due to the low incidence and prevalence, the diseases are included in the list of rare (orphan) diseases of the Russian Federation (edit dated June 23, 2021) [2]. Included in the register of rare nosologies in Europe — orphaned [3]. The prevalence of these diseases in Europe for IRP is 6-8 per 100 thousand [4], for AOSD — 0,16-0,4 per 100 thousand [5]. There are no publications assessing the prevalence of AOSD in Russia. The only article assessing the prevalence of IRP in the Russian Federation was published in January 2021 [6].

Currently, the globally recognized criteria used to confirm IRP are specified in the European Society of Cardiology recommendations on the diagnosis and management of patients with pericardial disease 2015 [4]. The diagnosis of recurrent pericarditis is verified if a recurrent episode of pericarditis occurs at least 4-6 weeks after the first episode of acute pericarditis has resolved. Confirmatory signs of pericarditis include clinical and instrumental data (typical retrosternal pain, new effusion into the pericardial cavity or worsening of the previous one, characteristic signs on the electrocardiogram), additional criteria of IRP, such as fever, pleurisy, increased acute phase values, neutrophilia, changes of liver values [7], are currently not obligatory, but serve as a clinical reference for IRP confirmation in disputed cases. However, it is possible to confirm the fact that recurrent pericarditis is *idiopathic* only by a broad differential search, which includes AOSD.

Due to the lack of diagnostic and pathognomonic markers in AOSD, >7 classifications of the disease criteria have been proposed, none of which has 100% sensitivity and specificity. Yamaguchi criteria with sensitivity of 96% and specificity of 92% are recognized as the most widely used classification criteria [8]. The criteria are divided into large and small. To confirm the AOSD diagnosis, 5 criteria should be scored, 2 of which are large, *provided* that other possible causes of pericarditis are excluded. Major criteria include fever >39° C, lasting more than <1 week, leukocytosis $10*10^9$/l, typical rash, and arthralgias for 2 weeks. Minor ones include sore throat, lymphoadenopathy and/or splenomegaly, altered liver tests, negative antinuclear factor and rheumatoid factor. Thus, if a patient's clinical picture is dominated by fever and serositis, and the laboratory parameters are dominated by neutrophilic leukocytosis, a slight increase in aminotransferases, negative indicators of antinuclear and rheumatoid factor, and the instrumental examination reveals moderate lymphoadenopathy, then even if there are no joint symptoms (arthralgia and arthritis) the AOSD diagnosis is legitimate.

Depending on the clinical picture, AOSD is usually subdivided into predominantly articular and predominantly systemic (including without damage to the musculoskeletal tract) forms, and according to the disease course, into monocyclic, polycyclic and chronic [9].

IRP and AOSD — diseases — exceptions. Paradoxically, in order to make a diagnosis of IRP, it is necessary to exclude AOSD, and vice versa. However, when we are talking about a systemic form of AOSD with serositis (as demonstrated in the example) — it becomes almost impossible.

Thus, the diagnosis of IRP and AOSD is complicated by a number of peculiarities:

1. Lack of specific biomarkers of the disease detected both during exacerbation and during remission.
2. Lack of known genetic mutations.
3. Non-specificity of symptoms (fever, serositis, arthralgia, myalgia).
4. Inability to confirm the diagnosis in the absence of signs of disease flare.
5. Presence of extracardiac manifestations in many patients with IRP, on the one hand, and manifestations of serositis in the structure of systemic variants of AOSD, on the other hand.

The above makes it urgent to carry out prospecting work to identify new markers of the disease.

Material and methods

The cross-sectional study included patients with IRP and AOSD over 18 years of age who were examined at the V.A. Almazov Scientific Research Center from 2018 to 2020. IRP was established according to the recommendations of the European Society of Cardiology for the Diagnosis and Management of Patients with Pericardial Diseases [4]. The AOSD diagnosis was confirmed on the basis of Yamaguchi classification criteria [8]. Patients was included during disease recurrence. The IRP recurrence was confirmed in the presence of all 3 symptoms — increase in C-reactive protein (CRP), new pericardial effusion or deterioration of the previous one and typical retrosternal pain. CRP was considered as recurrence when the CRP concentration was higher than the reference and at least 1 clinical symptom, which included arthritis, rash, pericarditis, and/or pleurisy. All participants signed voluntary informed consent to participate in the study. The study was approved by the Ethics

Table 1

Clinical and laboratory characteristics of patients with IRP and AOSD

Indicator (norms)	AOSD, n (%)	IRP, n (%)	p
Number of patients	15 (100%)	15 (100%)	
Gender (female/male)	12/3	11/4	
Age, years	28 [25;42]	55 [44;66]	
Fever	15 (100%)	15 (100%)	1
Pericarditis	6 (40%)	15 (100%)	<0,001
Pleurisy	5 (33,3%)	14 (93,3%)	0,001
Arthritis	13 (86,6%)	3 (20%)	<0,001
Arthralgia	13 (86,6%)	9 (60%)	0,099
Rash	12 (80%)	1 (6,6%)	<0,001
Lymphadenopathy	11 (73,3%)	4 (26,6%)	0,011
Splenomegaly	8 (53,3%)	0 (0%)	0,001
Hepatomegaly	5 (33,3%)	5 (33,3%)	1
Pharyngalgia	11 (73,3%)	4 (26,6%)	0,011
Leukocytes, $*10^9$/l, (4,0-9,0)	13,5 [8,4;17,4]	9,7 [8,2;12,8]	0,158
Neutrophils, $*10^9$/l, (2,00-5,80)	8,8 [4,8;13,4]	6,1 [5,0;9,0]	0,217
AST, U/l, (5,0-34,0)	24 [14;52,5]	26,0 [20,5;45,5]	0,650
ALT, U/l, (0,0-33,0)	61,3 [12;82]	41,0 [29,5;50,0]	0,801
CRP, mg/l, (0,0-5,0)	90 [25;160]	104,0 [57,0;170,0]	0,836
Ferritin, ng/ml, (13,0-150,0)	1416,5 [591;2000]	408 [239;643]	0,008
ESR, mm/h, (2-25)	47 [22;65]	55 [32;65]	0,684
Fibrinogen, g/l, (1,9-4,3)	4,5 [2,8;6,1]	4,6 [4,0;6,1]	0,442
GF, %, (⩾78,3% — normal, 30,5-78,2% — moderate decrease, ⩽30,4% — pronounced decrease)	12,0 [0,1;29,1]	33,9 [29;38]	0,067
IL-6, pg/ml, (0,0-10,0)	33,9 [10,7;56,7]	24,9 [9,9;43,3]	0,4
IL-18, pg/ml, (104,0-270,0)	2114 [1994;2127]	161,5 [120,8;285,2]	<0,001
IL-1, pg/ml, (0,0-11,0)	0,01 [0,01;0,77]	0,39 [0,01;1,03]	0,362
PCT, ng/ml, (0,0-0,05)	0,08 [0,03;0,22]	0,06 [0,05;0,09]	0,541

Abbreviations: AST — aspartate aminotransferase, ALT — alanine aminotransferase, AOSD — adult Still's disease, GF — glycosylated ferritin, IRP — idiopathic recurrent pericarditis, PCT — procalcitonin, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, IL-1 — interleukin-1, IL-6 — interleukin-6, IL-18 — interleukin-18.

Committee of the V.A. Almazov National Medical Research Center in St. Petersburg (No. 28, version 1.0 dated February 12, 2018).

Blood draw in all patients was performed in the morning in fasting state during recurrence of the main disease before the start of contradictory therapy.

The change in concentrations of IL-1, IL-6, IL-18, procalcitonin was performed using enzyme immunoassay (commercial kits manufactured by Vector-Best, Russia). Ferritin — by immunoturbidimetry on an AU-480 analyzer (Beckman Coulter, USA). The determination methodology for glycolized ferritin (GF) is described in the article by Potapenko VG, et al. 2018 [10]. Clinical blood tests, CRP and aminotransferases using standard commercial reagents.

Statistical analysis of the results was performed using Statistica 10.0 for Windows (StatSoft Inc., USA) and Prisma GraphPad 6.0 (GraphPad Software, USA). If an abnormal distribution was detected, the results were described as median and 25^{th};75^{th} percentiles. Mann-Whitney U-criterion was used to compare quantitative signs. Correlation analysis between the studied attributes was performed using Spearman's rank correlation coefficient (r_s). The significance criterion was set at the level of $p<0,05$.

Results

The study included 15 patients with AOSD, 15 with IRP. The median age in patients with AOSD was 28 years [25;42], IRP — 55 years [44;66]. Clinical and laboratory characteristics of the groups,

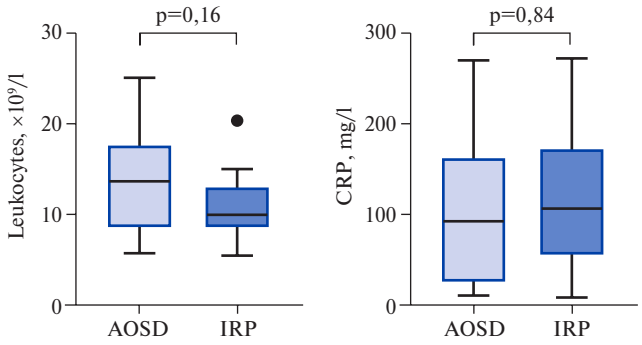

Figure 1. CRP concentration and the number of leukocytes in patients with AOSD and IRP.
Abbreviations: AOSD — adult Still's disease, IRP — idiopathic recurrent pericarditis, CRP — C-reactive protein.

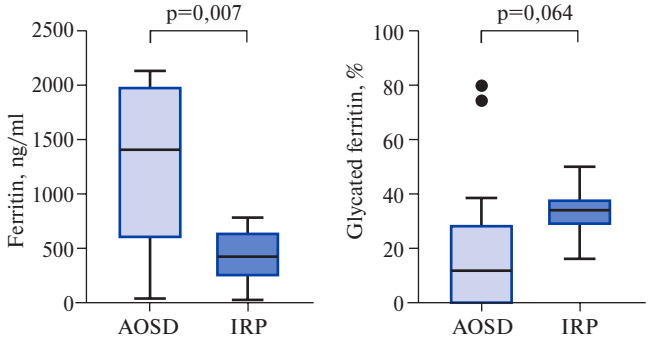

Figure 2. Comparison of ferritin concentration and percentage of GF in serum in patients with AOSD and IRP.
Abbreviations: AOSD — adult Still's disease, IRP — idiopathic recurrent pericarditis.

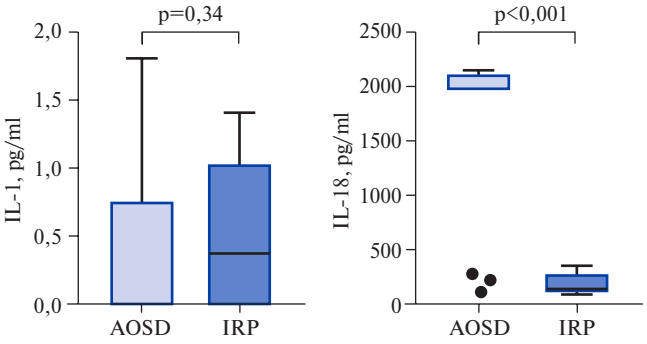

Figure 3. Comparison of IL-18 and IL-1 serum concentrations in patients with AOSD and IRP.
Abbreviations: AOSD — adult Still's disease, IRP — idiopathic recurrent pericarditis, IL-1 — interleukin-1, IL-18 — interleukin-18.

medians of analyzed parameters are presented in Summary Table 1.

Neutrophilic leukocytosis >10*10>⁹/l was detected in 10 patients with AOSD and in 9 patients with IRP. Median concentrations of acute phase markers, aspartate aminotransferase, alanine aminotransferase were elevated in all patients and were not statistically different in the studied groups. The CRP concentration and the number of leukocytes in the study groups are shown in Figure 1. Differences were found in the following indices — median age, ferritin concentration, GF and degree of IL-18 elevation.

Ferritin concentration is increased in both groups. In the AOSD group, the increase in ferritin concentration was statistically more significant (1416 pg/ml vs 408 pg/ml, p=0,008), as was the decrease in its glycosylated fraction (12% vs 33,9%, p=0,067) (Figure 2). The IL-6 and IL-18 concentrations were elevated in both groups, but the IL-18 concentration was statistically significantly higher in the AOSD group (2114 pg/ml vs 161,5 pg/ml, p⩽0,001) (Figure 3). The IL-1 concentration did not exceed the reference values and did not differ in the study groups (Figure 3).

In the correlation analysis, there was a direct correlation between IL-18, ferritin levels (r_s=0,73, p=0,03) in the AOSD group. No other correlations between clinical and laboratory parameters were found, probably due to the small sample size.

Discussion

According to the data obtained during the study, there were no differences in such indices as leukocyte count, absolute neutrophil count, erythrocyte sedimentation rate, CRP, and aminotransferases between the groups. This confirms the fact that it is impossible to distinguish between IRP and AOSD using standard diagnostic approaches. In the absence of established genetic predisposition, informative diagnostic laboratory tests, it is of interest to consider a broader panel of inflammatory biomarkers in order to assess their diagnostic significance.

Ferritin and GF. Normally, >78% of ferritin exists in glycosylated form. With increased synthesis of ferritin by cells (macrophages, Kupffer cells, hepatocytes, endothelium), glycosylation of the protein decreases, which leads to a change in the ratio of free ferritin and its glycosylated form in blood serum. In 2002, Fautrel B, et al. [11] proposed to use GF expressed as a percentage of total ferritin as a laboratory criterion for AOSD. The GF indicator ⩽20% is taken as a diagnostic value. The GF determination has not been performed in other AID. In the present study, the GF percentage in patients with IRP was investigated in a scientific first. According to the results obtained in the course of work, the percentage of GF in patients with IRP is reduced, a median rate was 33,9%. The decrease was less significant than in the AOSD group, where the GF median was 12%, which may be explained by fewer symptoms and less pronounced leukocytosis.

Cytokines. The IL-1 cytokine superfamily has 11 representatives. They are the most important regulators of inflammation, controlling various processes of innate immunity [12]. IL-1β and IL-18 synthesized in response to the inflammasome activation, a key mechanism in the development of AOSD and IRP, are of most interest. Blocking these targets in practice proved to be effective and formed the basis of anticytokine therapy [13, 14] in the treatment of both AOSD and IRP.

IL-1. IL-1 is divided into 2 independent cytokines — IL-1α and IL-1β, united by a common receptor (IL-1R1) and performing similar biological functions.

IL-1β has a central role in AID pathogenesis. Its importance has been confirmed by clinical studies in various AID using IL-1 blockers, where the percentage of responders exceeded 90% [13, 14].

Based on the data obtained in this study, no increase in serum IL-1β concentration was detected in either group. We can assume that the obtained results are underestimated for a number of reasons: first, the existing test systems work incompletely within the low IL-1β concentrations, and second, the cytokine's short half-life.

IL-18. IL-18 is one of the key cytokines synthesized in response to monocytic cell activation. Its significant increase was noted in diseases such as AOSD [15, 16], recurrent macrophage activation syndrome, macrophage activation syndrome associated with loss of NLRC4 function (NLRC4/MAS) [17] pyogenic arthritis, gangrenous pyoderma and acne (PAPA) [18]. A moderate increase was detected in infectious processes such as COVID-19 [19], sepsis [15].

There are no studies evaluating IL-18 concentrations in IRP, and the present study is the first to investigate IL-18 concentrations in patients with IRP. An increase in IL-18 concentration was detected in the studied groups, the concentration was higher in patients with AOSD, which correlated with the ferritin concentration. Our data are comparable with those of Priori R, et al. (2014) [15], where a correlation was found between IL-18 concentrations and ferritin. Her work also noted a correlation between disease activity and IL-18. This was not demonstrated in our cohort, which may be due to a smaller sample.

Colafrancesco S, et al. (2012) [16] demonstrated the relationship between IL-18 concentration and worse prognosis, disease activity, risk of macrophage activation syndrome.

Some authors hypothesized the possibility of using IL-18 as an additional AOSD diagnostic marker [20]. However, the accumulated data do not support this hypothesis. Probably, the determination of IL-18 concentration will find its application when using composite scales.

IL-6. Since the late 1990s, the study of IL-6 as a marker of AOSD activity began [21]. It was not considered as a diagnostic marker, because its increase was noted both in autoimmune diseases and in AID. Similar concentrations of this cytokine in infectious diseases have been shown, and its correlation with CRP level is known. This marker has not been studied in IRP.

In the cohorts we studied, IL-6 concentrations were comparable and correlated with CRP levels in both groups. Its determination in routine clinical practice is not justified due to insufficiently high specificity, but the study of its concentrations is valuable in terms of pathogenesis and prediction of response to therapy with IL-6 blockers.

Conclusion

As part of the study, we established a similar pattern of changes in inflammatory biomarkers in patients with AOSD and IRP, which is expressed in an increase in cytokines (IL-18, IL-6), ferritin. It was noted that the increase in IL-18 concentration was higher in the AOSD group, which may be explained by a more generalized inflammatory process.

If to consider AOSD and IRP on a continuum, a certain pattern can be observed: the younger the patient, the more systemic manifestations (arthritis, rash, splenomegaly), higher levels of ferritin and IL-18.

The obtained data are not sufficient to make an unequivocal statement about the general classification, molecular genetic and epigenomic studies in these conditions are required.

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