Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "Allergy Newsletter" which contains latest and interesting news in the field of allergy.

This issue contains:

1. **Investigation of Tic disorder in allergic rhinitis children and adolescents**
2. **Evaluation of association between IL-36 family cytokines in peripheral blood and assessment of subjective and objective results in patients with allergic rhinitis**
3. **Investigation of IL-1β and iNOS in enhancing asthmatic comorbidities and decreasing the lung function in perennial allergic rhinitis children**
4. **An uncommon case of atypical rash manifesting as persistent itchy urticaria**

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Looking forward to your valuable feedback
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Investigation of Tic disorder in allergic rhinitis children and adolescents

Introduction

Allergic rhinitis was more severe in patients with tic disorder than allergic rhinitis alone.

Allergic rhinitis(AR) is a prevalent non-communicable disease globally, affecting millions of people. It frequently occurs in conjunction with other health issues, including tic disorders. Tic disorders are characterized by involuntary or semi-voluntary motor movements, known as motor tics, or the production of sounds, referred to as vocal tics. These symptoms can also include Tourette syndrome. Tics are generally sudden, brief, repetitive, rapid, and meaningless, and they often occur unpredictably, typically beginning in childhood.[1] Children with tic disorders often experience a high incidence of allergic conditions such as allergic rhinitis, asthma, eczema, and allergic eye inflammation. Numerous studies have indicated a correlation between these allergic conditions and tic disorders, as well as attention deficit/hyperactivity disorder (TD/ADHD).[2] This study aimed to evaluate the link between tic disorders and allergic rhinitis in children and adolescents and to determine the underlying contributing factors.

Methods

A case control study was conducted in children and adolescents under 18 years old with allergic rhinitis and neurological tic disorders. Study group was divided into two groups which includes case group and control group. Case group included children and adolescents diagnosed with allergic rhinitis, exhibited symptoms of tic disorders, while control group included children and adolescents diagnosed with allergic rhinitis, without any symptoms of tic disorders or repetitive behaviours. Tic disorders were investigated using DSM-5 criteria for the classification of tic disorders.

Results

This study included 47 patients in case group and 47 patients in the control group. There was no statistically significant difference in gender between those with and without motor tics (P-value=0.125), however the majority of those with motor tics were men (11 individuals, or 68.75%). However, the majority of patients (22, or 52.38%) with vocal tics were female, and there was a statistically significant difference in gender between the two groups with and without vocal tics (P-value=0.026). The two groups with and without vocal tics had different histories of infantile eczema, patients without vocal tics had a higher prevalence of infantile eczema (n=35, or 83.33%). Furthermore, there was a statistically significant difference in food allergy in infancy between the two groups with and without motor tics (P-value=0.022) and vocal tics (P-value=0.024). Patients with sound tics had a significantly less history of middle ear infections (P-value=0.006). Compared to the control group, asthma was more prevalent overall. In the case group, episodes of the common cold and nocturnal cough during those

episodes occurred much more frequently. Patients experienced AR symptoms more days per week (P-value≤0.001; OR (every day vs. three days a week) =11.02(2.98, 40.76)) and took more medication for AR (P-value=0.0113; OR=5.02(1.31,19.21)) in the case group (Figure 1).

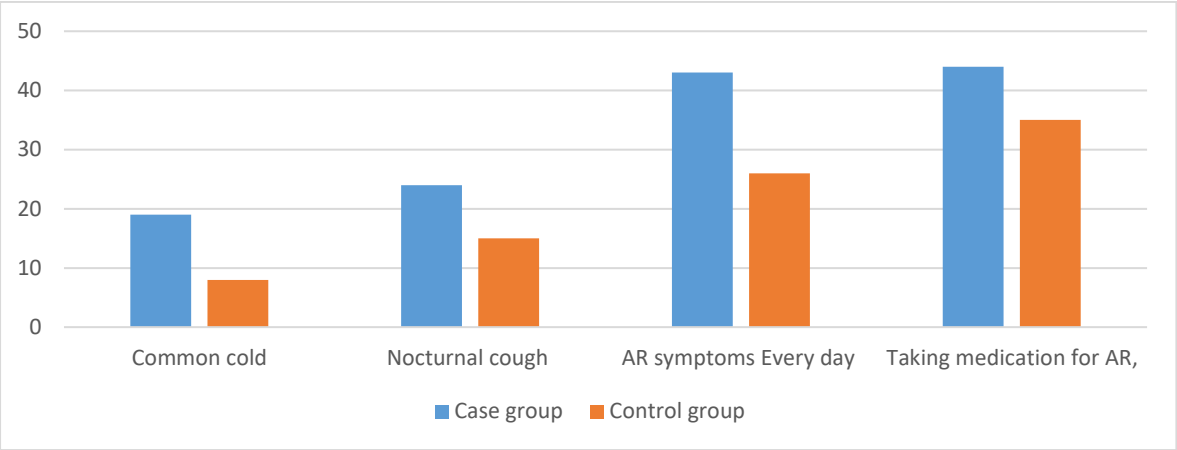

Figure 1. Comparison of clinical and laboratory findings in case and control group

Discussion

According to this study, provisional tic disorder accounted for 78.7% of all tic disorders diagnosed in individuals with allergic rhinitis, making it the most common tic condition among these patients. This result validated the findings of Jie hong Huang et al., who showed that tic disorders particularly provisional tic disorder was linked to allergy diseases and it also showed that allergic conditions such as allergic rhinitis were associated with tic disorders.[3] On the other hand, individuals experienced sound tics more frequently than motor tics (80.8% versus 34.04%, respectively). With respect to the neurological aspects of allergic rhinitis, studies indicated that the nervous system was crucial in controlling the major symptoms of rhinitis, including mucus secretion, congestion, and sneezing. A significant observation was the reduced prevalence of infantile food allergies in the majority of patients with sound tics. In 12.8%, 14.9%, and 27.7% of the cases history of sinusitis, conjunctivitis, and middle ear infection was present. Infections that required antibiotic prescriptions occurred in the early stages of life in 57.4% of all cases.[1] Previous studies has demonstrated that early infection exposure can increase a patient's subsequent chance of developing tic disorders.[4]

Conclusion

According to this preliminary investigation, the most prevalent diagnosis of tic among allergic rhinitis patients particularly those with motor tics was provisional tic disorder. Asthma in motor tics and among patients with vocal tics a history of food allergy in infancy, and a history of infantile eczema were common. Additionally, compared to those with rhinitis alone, patients with allergic rhinitis and tic had more severe symptoms (more symptoms per week). These results highlighted the connection between immune mechanisms and tic disorders.

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Evaluation of association between IL-36 family cytokines in peripheral blood and assessment of subjective and objective results in patients with allergic rhinitis

Introduction

IL-36α and IL-36β can be used as objective indicators to evaluate the severity of allergic rhinitis

Allergic rhinitis (AR), a common illness that affects 400 million people globally is a cause for concern as it's frequency is rising over time. Typically, AR coexists with other illnesses as asthma, which can have a serious negative financial impact as well as lower quality of life. It has been demonstrated that abnormally high Th2 cytokines are the source of AR, and new research on the cause indicates to a compromise in the integrity of the nasal epithelial barrier.[1] Increasing evidence suggest that the cytokines of the IL-36 family play a major role as mediators in a variety of inflammatory disorders and were closely related to the onset of disease. The peripheral serum of AR patients also contained significantly higher protein concentrations of IL-36 family cytokines than did normal controls, indicating that these cytokines may play a role in the pathophysiology of AR. However, it was unclear whether AR patients' levels of IL-36 family cytokines were related to the severity of their disease.[2] This study was conducted to investigate the correlations between IL-36 family cytokine levels and subjective and objective assessment results and to further examine the potential roles that cytokines from the IL-36 family in the development of AR.

Methods

About 77 patients with AR were included in this study. Inclusion criteria for the study involved patients aged 5 to 70 years with a confirmed diagnosis of allergic rhinitis (AR) and no other respiratory tract or allergic diseases. The 22-item sino-nasal outcome test (SNOT-22) score was used to assess bother-someness problems associated with AR symptoms and quality of life. Severity of illness visual analogue scale (VAS) score was utilized to assess the overall extent of AR symptoms, including nasal, ocular, and asthma-related symptoms. Blood samples were collected from the participants, and the concentration of IL-36 family cytokines was measured using enzyme-linked immunosorbent assay (ELISA). Correlation analysis was conducted to assess the relationship

between IL-36 family cytokine concentration levels and VAS scores, SNOT-22 scores, and other clinical parameters.

Results

Patients with AR had the highest concentration of IL-36α, IL-36Ra, IL-36γ, and IL-38 in their peripheral blood, whereas IL-36β had the lowest level (Figure 1). Spearman rank correlation analysis showed IL-36α level was positively correlated with IL-36γ, IL-36β level was positively correlated with IL-36Ra and IL-38, IL-36γ level was positively correlated with IL-36Ra and IL-36Ra level was positively correlated with IL-38 level. 49 out of 77 AR patients tested positive for total immunoglobulin E (tIgE) allergen, resulting in a 63.64% positive rate (49/77). It was found that IL-36α level was positively correlated with VAS score for nasal congestion symptoms, while IL-36β level was positively correlated with the total VAS score for ocular symptoms and VAS scores for ocular itching and eye pain symptoms. However, it was found that there was no correlation between the levels of all cytokines in IL-36 family and SNOT-22 score, the number of positive inhaled allergens, or the maximum positive intensity of allergen specific immunoglobulin E (sIgE).

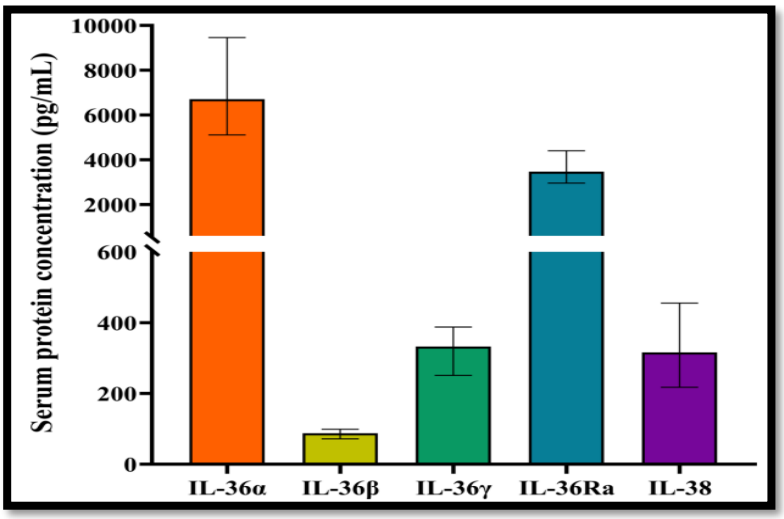

Figure 1. IL-36 family cytokines concentration in the peripheral blood of 77 patients with AR

Discussion

The study's findings demonstrated a weak positive connection (r=0.28, P=0.013) between the levels of IL-36α and IL-36γ in the peripheral blood of AR patients. It also showed that IL-36β level in peripheral blood was moderately correlated with the level of the IL-36R antagonist IL-36Ra (r=0.55, P<0.001). Additionally, there was a weak positive association between the levels of IL-36γ and IL-36Ra in peripheral blood. However, in this study, patients with AR had the lowest levels of IL-36β and the highest level of IL-36α in their peripheral blood.[2] Qin X et al. study reported compared to healthy controls, patients with AR had significantly increased peripheral blood protein concentrations of IL-36α, IL-36β, IL-36γ, IL-36Ra, and IL-38, with IL-36γ having the highest concentration.[3] Thus IL-36α and IL-36β levels were correlated with severity of AR and these could be used as objective indicators to assess the severity of AR.

Conclusion

The results of this study showed a correlation between the severity of the condition of patients with AR and the protein concentration levels of IL-36α and IL-36β cytokines in peripheral blood. As a result, IL-36α and IL-36β may be used as objective markers to assess the severity of AR.

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Investigation of IL-1β and iNOS in enhancing asthmatic comorbidities and decreasing the lung function in perennial allergic rhinitis children

Introduction

Elevated levels of IL-1β, iNOS, and vimentin in the serum were identified as significant indicators of comorbidity of perennial allergic rhinitis and asthma in children.

Asthma is a common chronic inflammatory condition in children and adolescents. Asthma and allergic rhinitis (AR) usually co-exist in same patient, in children as well as in adults. Around 38% of individuals with allergic rhinitis also have asthma, and 6% to 85% of those with asthma also have nasal symptoms.[1] Around 80% of the patients with perennial asthma have AR. Nitric oxide (NO) is an essential regulator of various physiological functions of airway epithelium. Increased levels of NO concentration by dysregulation of iNOS activity enhances chronic inflammatory responses and nitration of proteins which triggers bronchial epithelial tissue injury leading to various pulmonary diseases such as asthma.[2] This study aimed to evaluate the role of interleukin-1β (IL-1β), a pro-inflammatory cytokine, and inducible nitric oxide synthase (iNOS) in comorbidity of AR and asthma and in decline of lung function.

Methods

A nested case control study was conducted in a total of 240 participants with perennial AR (PAR) (PAR alone: 113 children, PAR and asthma: 127 children). Study included only PAR children, having an inflammatory process all year round. Diagnosis of AR was made on the basis of symptoms such as rhinorrhoea, nasal obstruction, nasal itching, and sneezing and objective tests of IgE-mediated allergies, such as the skin prick test. The enzyme-linked immunosorbent assay (ELISA) was used to evaluate serum levels of IL-1β (which indicates the activation of inflammasomes), CCL-24 (chemokines that produce eosinophils in allergic disorders) and the EMT marker. Furthermore, a NOS kit was used to measure the epithelial iNOS data. The study employed univariate and multivariate analyses to investigate potential associations between various variables and the onset of comorbidity and decreased lung function.

Results

Total IgE, eosinophil count, and vimentin did not vary significantly between the PAR alone group and the PAR and asthma group. The PAR and asthma group had significantly greater levels of IL-1β, CCL24, and iNOS, whereas E-cadherin was significantly lower. In both groups, Dermatophagoides pteronyssinus or Dermatophagoides farina had the highest number of positive allergies. Univariate analysis showed that IL-1β (>10.84 pg/ml), iNOS (>43.63 pg/ml), and vimentin (>486.0 pg/ml) were associated with the development of comorbidity of PAR and asthma (p= 0.003, 0.038 and 0.005, respectively), whereas according to multivariate analysis elevated levels of IL-1β (5.6- fold increase in risk) and high expression of iNOS and vimentin (6.3 and 7.9-fold increase in risk) were the significant risk factors for the development of comorbidity of PAR and asthma. Significantly higher levels of IL-1β, iNOS, and vimentin were seen in the group with decreased lung function (n=113) compared to the normal PFT (n=126). Decreased lung function was associated with IL-1β (>10.84 pg/ml), iNOS (>43.63 pg/ml), and vimentin (>486.0 pg/ml) in univariate analysis (p=0.027, <0.001, and 0.020, respectively). High expression of iNOS and vimentin (22.3 and 6.7-fold increase in risk), as well as elevated IL-1β (7.8-fold increase in risk), were found to be significant risk factors for the development of decreased lung function in multivariate analysis. Strongest risk factor for comorbidity and decreased lung function was elevated levels of iNOS. Vimentin or CCL-24 activation by IL-1β or iNOS can independently cause comorbidity or a decrease in pulmonary function in AR.

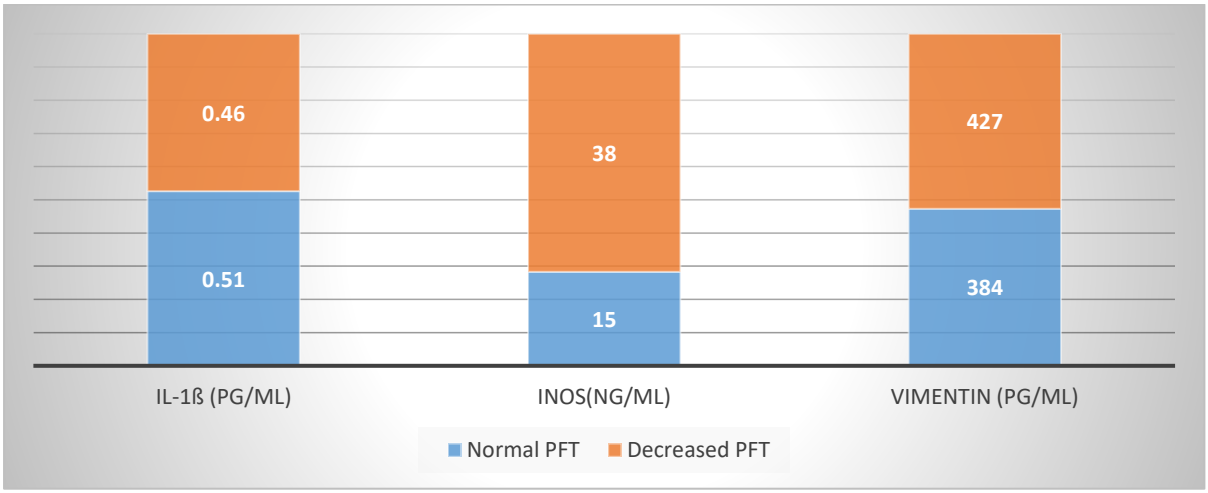

Figure 1. Biomarkers expression in normal lung function and decreased lung function groups

Discussion

This investigation found that children with greater IL-1β levels had an increased risk of AR and asthma comorbidity and decreased lung function.[2] Han MW et al. also showed that activation of IL-1β, a pro-inflammatory cytokine, might be a risk factor for moderate perennial AR and worsening of AR symptoms.[3] Furthermore, it has been determined that vimentin, a marker of airway remodelling, poses a risk for both comorbidity and decreased lung function. Moreover, in children with persistent AR, increasing IL-1β was linked to increased vimentin expression, indicating that IL-1β may initiate airway remodelling when comorbidity develops by activating vimentin. Based on its association with CCL, the study data suggested that iNOS

can be a risk factor for the comorbidity of asthma and PAR as well as decreasing lung function. In children with persistent AR, iNOS and IL-1β can both independently decrease lung function or cause comorbidity through interacting with airway remodelling biomarkers.[2]

Conclusion

According to this study, IL-1β and iNOS can be biomarkers in the development of PAR and asthma and decreased lung function, indicating possible areas for early detection and therapy.

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An uncommon case of atypical rash manifesting as persistent itchy urticaria

Introduction

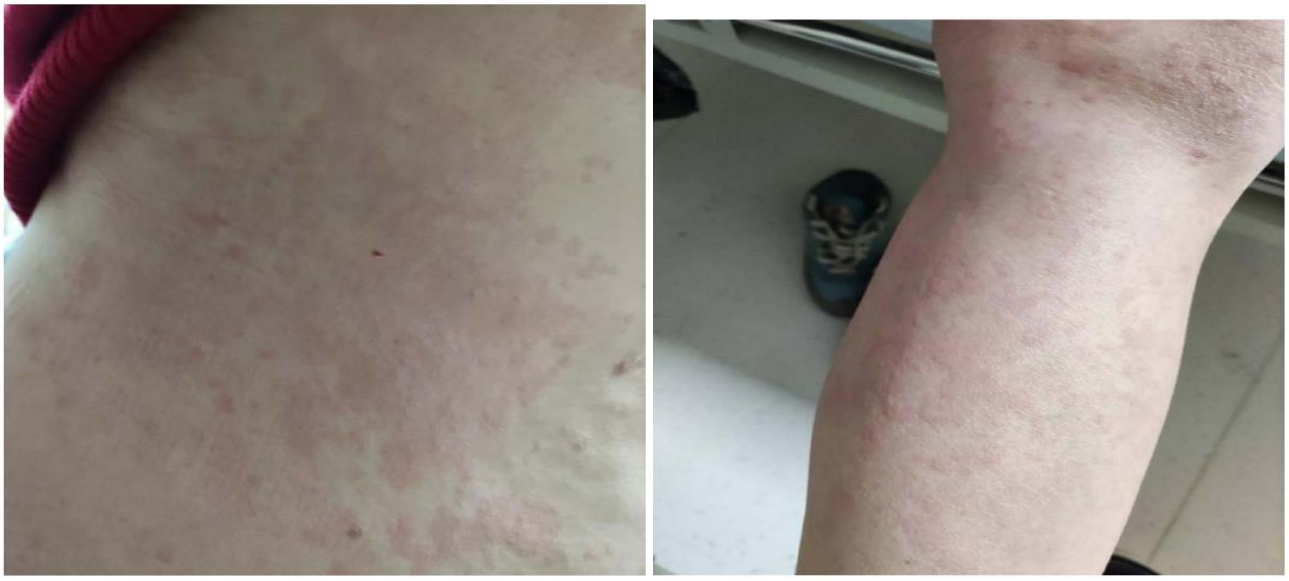
Typical rash and fever are the important diagnostic signs of adult-onset still's disease

Adult-onset Still's disease (AOSD) is a rare autoimmune condition with an unknown aetiology which is characterized by high fever, joint pain and non-pruritic rash. AOSD cases are rare with the prevalence of about 0.16/100,000 cases.[1] A definite diagnosis depends on the presence of the characteristic salmon-pink maculopapular rash. This common rash typically appears with fever and goes away as the fever goes down. It is typically asymptomatic. One of the key diagnostic criteria was the typical rash, which was quite significant. On the other hand, abnormal rashes in AOSD patients have been reported in more recent research.[2] This report described a case of an AOSD patient with an atypical rash, which was not related to fever, persisted for long time, and manifested as pronounced itchy urticaria.

Case presentation

A 57 years old female patient presented with a 6-day history of fever characterized by chills and fatigue. The patient's temperature was increased to 39°C. Despite of initial treatment, patient persistently experienced recurrent fevers peaking at approximately 39°C, most commonly in the evenings or at night. Upon admission to hospital on the second day patient developed an urticaria rash on her lower legs, accompanied by pronounced itching. Initially it was diagnosed an acute urticaria and treated with anti-allergic where there was no improvement. Subsequently, the rash spread to back and distal parts of limbs, with pronounced itching (Figure 1). No improvement was seen upon administration with cetirizine and calcium gluconate. Blood test indicated polymorphonuclear leukocytosis, with a white blood cell count

of 20.0 × 109 /L, predominantly composed of 94.6% neutrophils. Inflammatory markers were significantly elevated, with procalcitonin levels increased to 2.90 ng/mL, while high-sensitivity C-reactive protein levels rose rapidly to 92.85 mg/L. There was also a rise in coagulation indicators, such as fibrin degradation products and D-dimer, which registered at 80.30 and 27.89 μg/mL, respectively. Further, ferritin level was elevated beyond 2000 ng/mL and lactate dehydrogenase level raised to 329 U/L. Serology also showed elevated titers of hCMV-IgG (107.0 U/mL), Rubella IgG (41.3 IU/mL), and HSV-IgG (>30.0 index). EBV-VCA-IgG titer was significantly increased, surpassing 750.0 U/mL. For infection control, the patient received therapy of cefoperazone/sulbactam 1.5/1.5g as soon after admitted. Because of the ongoing fever and high infection markers, patient also received 0.4 g of moxifloxacin. The right axillary lymph nodes were found to be enlarged using lymph node ultrasonography, however there were no visible structural abnormalities. A bone marrow aspiration showed hypercellularity, but there was no evidence of acute leukaemia, non-Hodgkin's lymphoma, or myelodysplastic syndromes. Instead, bone marrow hyperplasia was normal. The patient had a rash, but it was accompanied by continuous urticaria that was quite itchy and did not appear to be related to a fever. Therefore, a conclusive diagnosis of AOSD has not yet been established despite only 4 criteria being met. Her liver function was discovered to be abnormal a few days later. When more than five of Yamaguchi's criteria were met, an AOSD diagnosis was obtained.



Meprednisone was injected intravenously at a dose of 40 mg every day. Her temperature returned back to normal the following day, and by the third, the rash had totally gone. Following discharge, the patient continued to take 32 mg of methyl prednisone orally. Methylprednisolone was gradually tapered down over the course of the following 6 months. A year's follow-up revealed no recurrence of the rash, a stable condition, and no relapse.

Figure 1. Urticaria patches on back and lower limbs

Discussion

AOSD, a rare multisystem inflammatory disorder with an unclear aetiology. The main clinical signs and symptoms are fever, arthritis, rash concurrent with fever, sore throat, lymphadenopathy, and hepatosplenomegaly. Yamaguchi or Fautrel standards were used in the

diagnosis of AOSD mainly in which both mention that it was necessary to exclude infection, tumor, blood system diseases and other diseases before diagnosis. Early detection was difficult and prone to misdiagnosis. A vital indicator in the diagnosis of AOSD was the typical rash. The patient in this case, however, did not appear to be feverish instead, the patient was presenting with a persistent, itchy rash resembling urticaria. In addition, the rash's distribution on the trunk and distal extremities differed from the typical AOSD rash in these areas.[2] Lee et al. described 36 cases with AOSD were diagnosed, out of which 28 presented with persistent rashes. Apart from being persistent, atypical rashes can manifest as various types. Some appear as rashes resembling urticarial cysts.[3] Ferritin and C-reactive protein levels were both markedly raised in this patient's auxiliary examination, with the ferritin level increase being more evident. Patients diagnosed with AOSD frequently have elevated ferritin and C-reactive protein levels. Fautrel B et al. reported that in AOSD patient's ferritin levels were higher than those with autoimmune disease.[4] Atypical skin characteristics may play a major role in the diagnosis of AOSD and may even be included in the diagnostic criteria.

Conclusion

This case highlighted the significance of considering typical rash and fever as an important diagnostic sign for AOSD. AOSD must be considered even in cases when the patient presents with an atypical skin rash.

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