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Distinguishment of parasite-infected children from pediatric inpatients with both eosinophilia and effusion

Ruixue Miao, MD[a,b], Yu Zhu, PHD[a,b,*], Zhiling Wang, MD[a,b], Shuanghong Luo, PHD[a,b], Chaomin Wan, PHD[a,b,*]

Abstract

Patients with both serous effusion and eosinophilia are rarely reported and geographically distributed; their early diagnosis is difficult.

According to the ultimate diagnosis, patients (≤14 years) in West China Second hospital with serous effusion and eosinophilia were divided into two groups including a parasitic group and a non-parasitic group. Clinical data were collected and analyzed between the two groups. Subsequently, significant measurement indicators were evaluated by receiver operating characteristic (ROC) curve to explore the optimal cut-off points for the most appropriate sensitivity and specificity.

A total of 884 patients were diagnosed with serous effusion and 61 of them displayed co-morbidity with eosinophilia during enrolled time. Among 61 patients, 34 patients had parasitic infection and 27 had non-parasitic diseases. There were statistical difference in effusion position, the levels of white blood cell count (WBC), eosinophil (EOS), EOS%, C-reactive protein (CRP) between parasitic group and non-parasitic group. ROC curve demonstrated that the areas under the curve of EOS count and EOS% were >80%, and the corresponding optimal cut-off values were 1.71×10^9/L and 25.6% for distinguishing between parasitic and non-parasitic infections in our patients.

This study provided a quantified index for potentially quick and convenient indicators of pediatric patients presenting with both eosinophilia and effusion. Eosinophils were helpful to improve the initial diagnosis with awareness of parasitic diseases. For the cases with EOS > 1.71×10^9/L or EOS% > 25.6%, parasitic infection should be considered and serological tests are recommended in our region.

Abbreviations: CRP = C-reactive protein, EOS = eosinophil, IVIG = intravenous immunoglobulin, KD = Kawasaki disease, ROC = receiver operating characteristic, WBC = white blood cell.

Keywords: effusion, eosinophilia, parasite, pediatrics

1. Introduction

Eosinophil is produced from hematopoietic stem cells in bone marrow[1] and subsequently is released to peripheral circulation and tissue-dwelling cells.[2] Eosinophil produces and stores numerous biological molecules such as cyto-stimulatory proteins, cytokines, and chemotactic peptides,[3] which play an important role in regulating immune responses and facilitating tissue repair and tissue damage.[1,4] Eosinophilia is defined as an elevation of the eosinophil count, usually above 0.5×10^9/L, which indicates an underlying disease condition. Eosinophilia is classified into three categories—hematologic (primary), secondary (reactive), and idiopathic (unknown).[5] A variety of diseases can cause secondary eosinophilia, the most frequent causes are parasitic worm infection, allergic reactions, drug reactions, and autoimmune diseases.[6]

In our clinical practice, eosinophilia was observed in children presenting with serous effusion including pleural effusion, pericardial effusion, and ascites, especially in cases of parasitic infection. The causes of such condition are various and identifying the etiology of each cases rack pediatrician's brain.[7,8] Comprehensive clinical information on eosinophilia and serous effusion co-morbidity is very important to better understand the disease spectrum and improve clinical diagnostic skills. Yet few studies explored the characteristics among pediatric patients with eosinophilia and serous effusion. We performed this study to analyze the clinical characteristics in children with both eosinophilia and effusion and to explore valuable indicators for initial screening by comparing characteristics between the parasitic group and non-parasitic group.

2. Patients and methods

Patients: Data from patients presenting with both serous effusion and eosinophilia were collected retrospectively from West China

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[a] Department of Pediatrics, West China Second Hospital, Sichuan University, [b] Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan, P.R. China.

[*] Correspondence: Chaomin Wan, (e-mail: wcm0220@126.com); Yu Zhu, Department of Pediatrics, West China Second Hospital, Sichuan University, No 20, 3rd section of Renmin South Road, Chengdu 610041, P.R. China (e-mail: zhuyu_wj@163.com).

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Second Hospital between January 2011 and December 2016. Serous effusions were determined by ultrasound, x-ray, and computed tomography. Eosinophilia was defined as an elevation of the eosinophil count, definitely above 0.5×10^9/L in the peripheral blood.[9]

Methods: The patients with both serous effusion and eosinophilia were classified into two subgroups according their final diagnosis. One was parasitic infection group and the other was non-parasitic diseases group. Parasite infections were diagnosed according to epidemiological history, clinical features, immunology, and biopsy. Clinical data including sex, age, WBC, EOS, EOS%, CRP, and the effusion position and encapsulated effusion were collected, retrospectively and analyzed between two groups. In order to explore valuable indicators as auxiliary examination for differential diagnosis, statistically significant outcomes were further evaluated for sensitivity and specificity by ROC curve, which is always used to evaluate the accuracy of potential diagnostic markers in clinical trials. The area under the curve is between 0.5 and 1.0. The closer the value is to 1.0, the better the diagnostic effect. In this study, we choose the indictors that the area under the curve is >0.8. When the area under the curve was the largest, the corresponding point was deemed the optimal cut-off value.

Statistical analysis: Data were presented as means ± standard deviation (SD) or the median and interquartile range. Significant differences among the groups were analyzed by using independent *t* tests or nonparametric test. Count data were presented as constituent ratios and analyzed by Fisher exact test. All data were analyzed with SPSS statistical software (version 20.0). A *P* value <.05 was considered statistically significant.

This study was approved by the Ethical Committee of West Second University Hospital. Informed consent was obtained from the patient for publication of this case report and accompanying images.

3. Results

From 2011 to 2016, a total of 884 patients had serous effusion in hospital. Sixty-one (6.9%) patients were eosinophilia and serous effusion co-morbidity in this study, and 34 cases of them were diagnosed as parasite infections including 30 cases of paragomimiasis, three of myiasis and one hydatid infection. The remaining 27 cases were assigned to the non-parasitic group, where 22 patients were diagnosed with respiratory system infection caused by mycoplasma, EB virus, tuberculosis, and other uncertain pathogens and three cases were diagnosed with pericarditis caused by enterococcusfaecium or nonspecific pathogens and two children were diagnosed with Kawasaki disease (KD). The disease distribution of the participants is shown in Table 1.

Table 1

The disease distribution between parasite group and non-parasites group.

	Disease	n (%)
Parasite group		34
	Paragomimiasis	30 (88%)
	Myiasis	3 (9%)
	Hydatid disease	1 (3%)
Non-parasite group		27
	Respiratory system infection	22 (82%)
	Mycoplasma infection	7
	EB virus	3
	Tuberculosis	1
	Uncertain pathogen	11
	Pericarditis	3 (11%)
	Kawasaki disease	2 (7%)

The statistically significant difference ($P < .05$) was found in effusion position, WBC count, the count and ratio of EOS, and the level of CRP in peripheral blood between the two groups. The ratio of multiple serous effusions in the parasite group (67.65%) was higher than in the non-parasitic group (11.11%). More bilateral pleural effusions appeared in the parasite infections group (76.47%) rather than the non-parasite group (22.22%). In addition, the levels of WBCs (13.16 ± 4.91/mm^3), EOS (4.5 [2.0,9.0]/mm^3), and EOS% (36.98% ± 19.34%) in peripheral blood were significantly higher in the parasite group compared with the non-parasite group (9.88 ± 3.63/mm^3; 1.0 [0.85,1.42]/mm^3; 15.56% ± 10.84%). However, the level of CRP (4.5 [1.8,12]mg/L), an indicator of acute inflammation, was lower in the parasite group (27 [4,66]mg/L), indicating indirectly that the parasitic infection was likely a chronic disease. There were no detectable differences in patient characteristics with regard to age, sex, and the aspects of the encapsulated effusion. Results are displayed in Table 2.

Further evaluations of the WBC levels, the count and ratio of EOS and the levels of CRP were performed by the ROC curve

Table 2

Comparison of clinical indicators between parasite group and non-parasite group.

	Parasite group (n = 34)	Non-parasite group (n = 27)	*P*
Count dates (n)			
Sex (F/M)	25/9	22/5	.594
Effusion position (S/M)	11/23	24/3	.000*
Encapsulated effusion (yes/no)	3/31	2/25	1.000
Pleural effusion (U/B)	6/26	13/6	.000
Measurement dates [X ± SD/M(P_{25}, P_{75})]			
Age (years)	6.97 ± 3.46	6.38 ± 3.87	.583
WBC (/mm^3)	13.16 ± 4.91	9.88 ± 3.63	.005
EOS%	36.98% ± 19.34%	15.56% ± 10.84%	.000*
EOS (/mm^3)	4.5 (2.0,9.0)	1.0 (0.85,1.42)	.000*
CRP (mg/L)	4.5 (1.8,12)	27 (4,66)	.016*

CRP = C-reactive protein, EOS = eosinophil, F/M = female/male, S/M = single/multiple, U/B = unilateral and bilateral, WBC = white blood cell.
* $P < .05$.

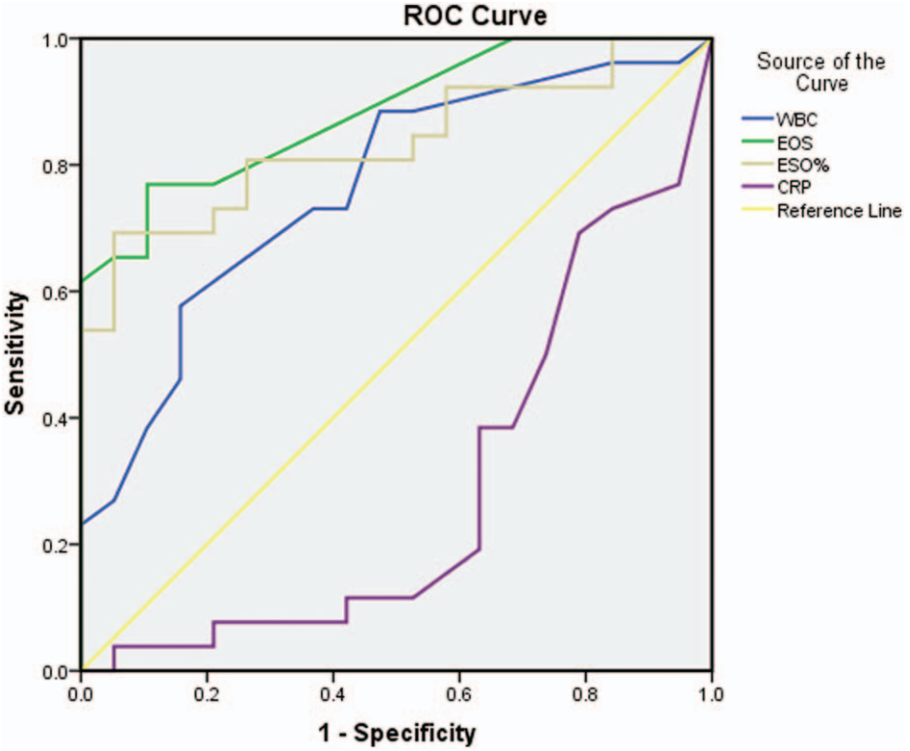

Figure 1. The ROC curve of statistically significant indicators (WBC, EOS, EOS%, CRP). The area under the curve of WBC, EOS, EOS%, and CRP were 0.884, 0.834, 0.762, and 0.288, respectively.

analysis. Results demonstrated that the areas under the curve for EOS count and EOS% were >80% and the cut-off points of EOS count and EOS% were 1.71×10^9/L and 25.6%, respectively. The corresponding sensitivity and specificity were 76.9% and 89.5% when EOS count was more than 1.71×10^9/L, and the corresponding sensitivity and specificity were 69.2% and 94.7%, respectively when EOS% was more than 25.5%. The results of ROC curve is presented in Figure 1 and Table 3.

4. Discussion

Patients presenting with both serous effusion and eosinophilia are rarely reported, especially in children. But in Southwest China region with high prevalence of parasitic diseases, these symptoms are common. In this study, 61 (6.9%) pediatric patients in total 884 cases with effusion displayed eosinophilia simultaneously. The diagnosis directions of the population always confuse pediatricians because the symptoms can be caused by different diseases without specificity. Guideline of the British Committee for Standards in Haematology (BCSH) reviewed that the causes of eosinophilia are numerous involving allergic disorders, drug-induced eosinophilia, infectious diseases, vasculitides, rheumatological diseases, hematological neoplasms, etc.[9] In our study, results demonstrated that the etiologies leading to eosinophilia and serous effusion were diverse, parasitic infection was the most common disease, up to 56%. Three kinds of parasitic (worm) infection were found in this study, they were paragonimiasis, myiasis, and echinococcosis. In parasite infection, eosinophilia is driven by IL-5-triggered degranulation, promoting the release of proteins involved in cytotoxicity and parasite killing[10–12] and increasing pathological damage to healthy tissue.[13] The migration of the parasitic worm causes damage to mesothelial cells resulting in serous effusion.[14]

Except for parasite infection, results shown that the presentation of both eosinophilia and effusion also was found in children with pneumonia caused by mycoplasma, EB virus, in children with tuberculosis, in children with pericarditis caused by enterococcusfaecium or nonspecific pathogens and in children

Table 3

The results of ROC curve.

	EOS ($\times 10^9$/L)	EOS%	WBC ($\times 10^9$/L)	CRP (mg/L)
The area under curve	0.884	0.834	0.762	0.288
Youden index	0.664	0.550	0.411	−0.439
Sensitivity (%)	76.9	69.2	88.5	19.2
Specificity (%)	89.5	94.7	52.5	36.8
Cutoff value	1.71	25.6	8.95	17.0

The areas under the curve of the count of EOS and EOS% were >80%.

The areas under the curve of the count of EOS and EOS% were 88.4% and 83.4%, respectively and the sensitivity and specificity were 76.9%, 89.5%, and 69.2%, 94.7%. The optimal cutoff values were 1.71×10^9/L and 25.6%, respectively.

with KD. While these diseases were common in the pediatric department, the condition with both eosinophilia and serous effusion leading by those diseases was uncommon. The association between eosinophilia and effusion across non-parasitic diseases and the pathological mechanisms are unclear and they were only reported sparsely. Literature has shown that mycoplasma infection-induced eosinophilia may triggered angioedema and thromboembolism.[15,16] In addition, some reports pointed out that the level of eosinophil was markedly distinct before and after intravenous immunoglobulin (IVIG) treatment in the acute stage of KD, illustrating that eosinophilia may indicate the IVIG-response of KD patients.[17] However, these situations indeed increase the difficulties in the processing of diagnosis.

In the processing of parasitic infection diagnosis, detailed epidemiological history (living area, close contact with animal, and crab consumption) are critical. Unfortunately, the detailed history is not always readily available to pediatricians, particularly considering the incomplete expression and memory of young children.[18] In order to distinguish quickly parasite infection from other diseases in the patients with serous effusion and eosinophilia, reliable indicators are necessary. In this study, we analyzed the difference between parasitic group and non-parasitic group. Results demonstrated that parasite infections were more prone to multiple serous and bilateral pleural effusions compared with the non-parasitic diseases, non-parasite diseases mainly presented in single position effusion except for EB virus infection-induced pericardium and pleural effusion. In addition, the parasite group presented a higher level of WBC, EOS, and EOS% than non-parasitic group. These findings could be helpful for the initial stage diagnosis when pediatricians encountered children presenting with effusion and eosinophilia.

To validate the potential indicators' role in distinguishing parasite infection from other etiologies in patients with both eosinophilia and effusion, ROC curves was conducted for the indicators WBC, CRP, EOS, and EOS%. Results showed that the areas under the curve for EOS and EOS% were >80%. When $EOS > 1.71 \times 10^9/L$ or $EOS\% > 25.6\%$, parasitic infection should be considered and further serological tests were recommended. Although eosinophilia is common in parasite infection, especially in worm infection, this study provided a quantified index for potentially quick and convenient indicators for pediatric patients presenting with both eosinophilia and effusion simultaneously.

4.1. Limitations

This is a retrospective study performed in single center. The indicators described need to be further verified in larger and multi-center populations through prospective studies. Future researches should also focus on achieving long-term follow-up to ascertain the validity of the associations.

5. Conclusions

The underlying diseases presenting with both eosinophilia and effusion were diverse including parasite infection, respiratory system infection caused by mycoplasma, EB virus, tuberculosis and KD in pediatric patients of southwest China. Among them, parasite infection was the most common disease. Patients with parasitic infections were more prone to serous and bilateral pleural effusion, and they presented higher levels of WBC, EOS, and EOS% in peripheral blood than other patients. When $EOS > 1.71 \times 10^9/L$ or $EOS\% > 25.6\%$ were shown in the patients with both eosinophilia and effusion, parasitic infection should be considered and further serological tests recommended.

Author contributions

Conceptualization: Yu Zhu, Shuanghong Luo, Chaomin Wan.
Data curation: Ruixue Miao, Yu Zhu, Zhiling Wang.
Formal analysis: Ruixue Miao, Shuanghong Luo.
Funding acquisition: Ruixue Miao.
Investigation: Ruixue Miao, Zhiling Wang, Shuanghong Luo, Chaomin Wan.
Methodology: Ruixue Miao, Yu Zhu, Shuanghong Luo, Chaomin Wan.
Project administration: Chaomin Wan.
Resources: Shuanghong Luo.
Supervision: Zhiling Wang, Chaomin Wan.
Writing – original draft: Ruixue Miao, Shuanghong Luo.
Writing – review & editing: Yu Zhu, Chaomin Wan.

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