Clinical analysis of hypereosinophilic syndrome first presenting with asthma-like symptoms

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ABSTRACT

Introduction: Clinical manifestations of hypereosinophilic syndrome (HES) are diverse. This study aimed to summarise these clinical characteristics with asthma-like onset as the first symptom, and compare these characteristics and treatment strategies between idiopathic and parasitic HES.

Materials and methods: We retrospectively analysed 36 HES patients with asthma-like symptoms as the first episode, between January 2013 and October 2019. Data of patients with HES of an unknown cause (idiopathic HES) and parasitic infection (parasite HES) were analysed.

Results: The idiopathic and parasite HES groups included 16 and 20 patients, respectively, with more males in the parasite HES group (p < .05). Wheezing and dry rales was the most common symptom and signs, with no significant differences in symptoms and signs between the groups. The most often misdiagnosed disease was bronchial asthma. The peripheral blood eosinophil count was significantly increased compared with normal counts in both groups (p > .05). Abnormal pulmonary function is mainly manifested as obstructive ventilatory disorder and mixed ventilatory disorder. Chest computed tomography showed extensive ground-glass exudation, patches, consolidation, nodules, and pleural effusion. Histopathological examination showed eosinophilic infiltration without vasculitis or granuloma. Glucocorticoids had a significant therapeutic effect, and the parasite HES group required combined deworming drugs. The duration of corticosteroids therapy in the idiopathic HES group was significantly longer than that in the parasite HES group (p < .05). The overall prognosis was good, and 81.25% of the patients were clinically cured in the parasite HES group; however, relapse occurred easily in the idiopathic HES group.

Conclusions: Asthma-like symptoms, obstructive ventilatory disorder or positive bronchial dilation test, and poor response to inhaled corticosteroids are not necessarily indicative of refractory asthma; HES should be considered. The clinical characteristics of HES of different aetiologies are similar. Systemic corticosteroid therapy is preferred for idiopathic and parasitic infections. Idiopathic HES is treated with prolonged corticosteroids and relapses easily.

KEY MESSAGES

- Asthma-like symptoms, obstructive ventilatory disorder or positive bronchial dilation tests, and poor responses to inhaled corticosteroids are not necessarily indicative of refractory asthma, and hypereosinophilic syndrome should be considered.
- The clinical characteristics of hypereosinophilic syndrome of different aetiologies are similar, and systemic glucocorticoid therapy is preferred for both idiopathic and parasitic infections.
- Idiopathic hypereosinophilic syndrome is treated with prolonged corticosteroids and relapses easily.

Abbreviations: HES: Hypereosinophilic syndrome; EOS: eosinophils; HESUS: idiopathic hypereosinophilic syndrome; HESp: primary hypereosinophilic syndrome; HESS: secondary hypereosinophilic syndrome; AHR: airway hyperresponsiveness; ECG: electrocardiography; IgE: immunoglobulin E; BDT: bronchial dilation test; CT: computed tomography; COPD: chronic obstructive pulmonary disease; BALF: bronchoalveolar lavage fluid; ICS: inhaled corticosteroids; ABPA: Allergic bronchopulmonary aspergillosis

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Introduction

Hypereosinophilic syndrome (HES) is characterised by persistently elevated levels of eosinophils (EOS), their infiltration into various tissues and organs, and the emergence of corresponding clinical symptoms and signs; the clinical manifestations are complex and diverse. In 2011, the Working Conference on Eosinophil Disorders and Syndromes referred to any hypereosinophilia associated with organ damage as HES, clearly defining idiopathic hypereosinophilic syndrome (HESUS), primary hypereosinophilic syndrome (HESp), secondary hypereosinophilic syndrome (HESs), and other conditions and syndromes [1]. Because HESUS is diagnosed by exclusion, it is difficult to rapidly and effectively diagnose in a clinical setting. One of the most common causes of HESp is parasite infection, which is often ignored and may lead to multiple organ failure [2,3].

Eosinophil-related respiratory diseases are a global concern, and patients can have a variety of clinical characteristics. EOS located in the airway can cause chronic inflammation (e.g. asthma and COPD), while EOS can also significantly increase in peripheral blood EOS (even as one of the diagnostic criteria, such as allergic bronchopulmonary aspergillosis [ABPA] and eosinophilic granulomatosis with polyangiitis [EGPA]) [4]. Although HES often involves the respiratory system, eosinophilic pneumonia and pleural effusion were the most common in previous reports [5]. However, HES with airway hyperresponsiveness (AHR), such as repeated wheezing attacks as first symptoms, and with obstructed but reversible pulmonary functions, is rare and garners little attention. Patients are often misdiagnosed as refractory bronchial asthma, resulting in long-term misdiagnosis and mistreatment, and even death. To improve our understanding of the clinical diversity of HES, we aimed to retrospectively analyse the clinical features of HES with asthma-like symptoms as the initial symptom, and compare the differences in clinical features between idiopathic and parasitic HES.

Materials and methods

Clinical data

We retrospectively analysed patients with HES who had initially presented with asthma-like symptoms between January 1, 2013 and October 1, 2019 at our institution. The basic condition, clinical data, and follow-up data of the patients were collected and statistically analysed. According to the strict regulations on a retrospective study of the Ethics Committee of the first affiliated Hospital of Guangxi Medical University, written informed consent was obtained in all cases (signed by the patient or their immediate family) prior to the study, and the approved ethics was 2021.KY-E-091.

Inclusion criteria

We included patients who met the following diagnostic criteria [1]: EOS count $>1.5 \times 10^9/L$ on two blood examinations (interval $\geq 1$ month); $\geq$ two organs damaged and/or dysfunctional, attributed to tissue hypereosinophilia; patients with systematic examination results, except for organ damage or dysfunction caused by other diseases or conditions; negative ETV6-PDGFRb, FIP1L1-PDGFRa, FGFR1, and JAK2 gene tests; and haematologist consultation records excluding HESp. The asthma-like symptoms include paroxysmal cough or wheezing. The patients with unknown causes were assigned to the idiopathic HES group, while those with clear parasitic infection were assigned to the parasite HES group.

Statistical analyses

Statistical analyses were performed using SPSS software (Windows version 25.0; SPSS Inc., Chicago, IL, USA). Continuous variables are represented as medians (interquartile range), categorical variables are expressed as counts (%), measurement data used rank-sum test (Wilcoxon rank-sum test or signed rank-sum test) for comparison between groups, and count data were analysed using the chi-square test or Fisher’s exact test for comparison between groups. Statistical significance was defined as a $P$-value of $<.05$.

Results

General data and clinical features

A total of 44 idiopathic HES and 34 parasitic HES cases were identified, of which 36 patients with asthma-like symptoms as the initial symptom were included in this study (16 [36.36%] patients in the idiopathic HES group and 20 [58.82%] in the parasite HES group). There was no statistical difference in age of onset between the two groups. There were more males than females in the parasite HES group ($p < .05$, Table 1), with a male-to-female ratio of 17:3. The median time from symptom onset to diagnosis was 2 (1–10.5) months in the idiopathic HES group and 6 (1–12)
months in the parasite HES group. There were no significant differences in the symptoms and signs between the two groups. Patients were misdiagnosed with bronchial asthma, pneumonia, chronic obstructive pulmonary disease (COPD), lung neoplasms, tuberculosis, and pulmonary embolism (Table 1). All cases showed multiple systemic involvements. Vascular and skin involvement were found in five cases, respectively. Cardiovascular examination results of electrocardiography (ECG) and echocardiography were abnormal in 10 cases. Five patients had abnormal digestive system examination results. Lymph node enlargement was observed in eight patients. In the parasite HES group, parasite eggs in the stool were found in all patients.

**Laboratory results, pulmonary function, and imaging**

Despite the elevated or abnormal results, there were no significant differences in the peripheral blood EOS count, erythrocyte sedimentation rate, C-reactive protein, immunoglobulin E (IgE), and myocardial enzyme levels between the two groups (Table 2). Tumour markers, immunoglobulins, and autoantibodies were normal in all cases, including anti-neutrophil cytoplasmic antibodies (ANCA).

One patient had pericardial effusion. Colour ultrasound showed ascites, hepatosplenomegaly, superficial lymph node enlargement, and superficial venous thrombosis. Thirty-one patients completed the pulmonary function examination, of whom eight showed normal results (because of the serious condition, they all completed the examination after treatment). There were 23 patients with abnormal pulmonary function, of whom eight were positive for bronchial dilation test (BDT). There were no significant differences in pulmonary function between the two groups. High-resolution chest computed tomography (HRCT) was performed in all cases, and the results showed extensive ground-glass exudation, patches, consolidation, nodules, pulmonary embolism, and pleural effusion

### Table 1. General data and clinical features of patients in idiopathic HES and parasite HES groups.

| Clinical features       | Idiopathic HES group (n = 16) | Parasite HES group (n = 20) | P value |
|-------------------------|-------------------------------|----------------------------|---------|
| Age (y)                 | 46.5 (35.25–51.00)            | 54.50 (35.75–64.75)        | .067    |
| Male                    | 8 (50%)                       | 17 (85%)                   | .034*   |
| Female                  | 8 (50%)                       | 3 (15%)                    | .190    |
| Wheeze                  | 14 (87.50%)                   | 20 (100%)                  | .900    |
| Cough                   | 16 (100%)                     | 17 (85%)                   | .238    |
| Expectoration           | 11 (68.75%)                   | 12 (60%)                   | .731    |
| Chest tightness         | 4 (25%)                       | 6 (30%)                    | .1000   |
| Chest pain              | 3 (18.75%)                    | 6 (30%)                    | .700    |
| Erythra                 | 4 (25%)                       | 1 (5%)                     | .149    |
| Dry rale                | 14 (87.50%)                   | 16 (80%)                   | .672    |
| Moist rales             | 3 (18.75%)                    | 3 (15%)                    | .1000   |
| Mediagnosis             |                               |                            |         |
| Bronchial asthma        | 12 (75%)                      | 16 (80%)                   | 1.000   |
| Pneumonia               | 5 (31.25%)                    | 8 (40%)                    | .731    |
| Chronic obstructive pulmonary disease (COPD) | 0 (0) | 4 (20%) | .113 |
| Lung neoplasms          | 1 (6.25%)                     | 1 (5%)                     | 1.000   |
| Pulmonary tuberculosis or tuberculous pleurisy | 0 (0) | 2 (10%) | .492 |
| Pulmonary embolism      | 3 (18.75%)                    | 0 (0)                      | .078    |
| Median time from onset of symptoms to diagnosis (M) | 2 (1–10.5) | 6 (1–12) | .328 |

Data are expressed as the number and percentage or median (interquartile range). *P < .05 is statistically significant.

### Table 2. Comparison of laboratory examination results between idiopathic HES and parasite HES groups.

| Laboratory examination                  | Idiopathic HES group (n = 16) | Parasite HES group (n = 20) | P value |
|-----------------------------------------|-------------------------------|----------------------------|---------|
| White blood cell (10^9/L)               | 11.11 (7.73–15.56)           | 10.04 (8.41–17.53)         | .799    |
| Eosinophil (10^9/L)                     | 2.37 (1.76–4.54)             | 2.13 (1.84–6.17)           | .633    |
| Partial pressure of oxygen (mmHg)       | 77.90 (67.08–83.18)^a         | 76.20 (70.75–78.70)^b      | .763    |
| Partial pressure of carbon dioxide (mmHg)| 36.55 (32.6–40.03)^a         | 40 (36.65–41.9)^b          | .025^a  |
| Immunoglobulin E (IU/mL)                | 322.4 (131.4–750.4)^c         | 489.8 (24.8–1000.7)^d      | .855    |
| Erythrocyte sedimentation rate (>20mm/H) | 7 (43.75%)                  | 7 (35%)                    | .734    |
| C-reactive protein(>10mg/L)             | 6 (37.5%)                    | 6 (30%)                    | .729    |
| Lactate dehydrogenase (>245 U/L)        | 9 (56.25%)                   | 11 (55%)                   | 1.000   |

*P < .05, statistically significant. Data are expressed as the number and percentage or median (interquartile range). References: Leucocyte: 3.5–9.5 × 10^9/L; Eosinophil: 0.02–0.52 × 10^9/L. Immunoglobulin E: 0–100 U/mL; The reference critical values of the other indicators are all values in parentheses. EOS, eosinophils; idiopathic HES group, patients with HES of an unknown cause; parasite HES group, patients with parasitic infection.
Ground-glass exudation was more commonly observed in the idiopathic HES group than in the parasite HES group ($p < .05$) (Table 3).

**Cytology and histopathology**

All patients were examined by bone marrow cytology or bone marrow biopsy. ETV6-PDGFR $\beta$ and FIP1L1-PDGFR $\alpha$ gene results, and FGFR1 and JAK2 genes results, were negative in five patients. Pathological examination of the bone marrow tissue confirmed greater infiltration of EOS, and smears showed an EOS proportion of $>20\%$ in 19 cases. Tissue biopsies from the lung, pleura, lymph node, and skin tissues all showed high infiltration of EOS, and no fibrinous necrotising vasculitis or necrotising granuloma (Figure 2). In addition, many EOS were found in bronchoalveolar lavage fluid (BALF) smears and pleural effusion smears. Positive EOS in pleural fluid is defined as a pleural effusion that contains $\geq 10\%$ eosinophils [6]. Positive EOS in bronchoalveolar lavage fluid is defined as containing $\geq 5\%$ eosinophils [7] (Table 4).

**Treatment and outcomes**

Fourteen patients in the idiopathic HES group were administered corticosteroids, with an initial dose of prednisone 20–80 mg/day. In the parasite HES group,

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*Figure 1.* Chest CT showing patches and consolidation, and bilateral pleural effusion. The lesion disappears after applying glucocorticoid combined with deworming drugs. (A,D) before treatment, (B,E) after 7 days of treatment, (C,F) after 7 weeks of treatment (patients from the parasite HES group). Chest CT showing extensive ground-glass exudation and patches shadow in both lungs, the lesion is gradually absorbed after glucocorticoid therapy: (G) before treatment; (H) after 2 days of treatment; (I) after 5 days of treatment; (J) after 9 weeks of treatment (patients from the idiopathic HES group). Chest CT shows pulmonary embolism (K) and nodule (L). CT, computed tomography; HES, hypereosinophilic syndrome.
Table 3. Comparison of imaging examination results between idiopathic HES and parasite HES groups.

|                                | Idiopathic HES group (n = 16) | Parasite HES group (n = 20) | P value |
|--------------------------------|-------------------------------|-----------------------------|---------|
| Abnormal cardiac ultrasound    | 0 (0)                         | 1 (5%)                      | 1.000   |
| Peritoneal effusion            | 0 (0)                         | 1 (5%)                      | 1.000   |
| Hepatomegaly/splenomegaly      | 0 (0)                         | 2 (10%)                     | .492    |
| Superficial lymph node enlargement | 2 (12.5%)                  | 2 (10%)                     | 1.000   |
| Peripheral venous thrombosis   | 2 (12.5%)                     | 0 (0)                       | .190    |
| Abnormal pulmonary function    | 10/14 (71.42%)                | 13/17 (76.41%)              | 1.000   |
| Obstructive ventilatory disorder | 5 (35.71%)                  | 10 (58.82%)                 | .285    |
| Mixed ventilatory disorder     | 5 (35.71%)                    | 3 (17.65%)                  | .412    |
| Diffusion disorder             | 6 (42.86%)                    | 5 (29.41%)                  | .447    |
| Bronchial dilation test positive | 3 (21.43%)                  | 5 (29.41%)                  | .698    |
| Chest CT or CTPA               |                               |                             |         |
| Ground-glass shadow            | 9 (56.25%)                    | 2 (10%)                     | .004*   |
| Patches or solid shadows       | 8 (50%)                       | 11 (55%)                    | 1.000   |
| Mass, nodular shadow           | 3 (18.75%)                    | 5 (25%)                     | .709    |
| Pleural effusion               | 5 (31.25%)                    | 6 (30%)                     | 1.000   |
| Pericardial effusion           | 0 (0)                         | 1 (5%)                      | 1.000   |
| Mediastinal lymph node enlargen | 1 (6.25%)                     | 3 (15%)                     | .613    |
| Pulmonary embolism             | 3 (18.75%)                    | 0 (0)                       | .078    |

Idiopathic HES group, patients with HES of an unknown cause; parasite HES group, patients with parasitic infection. CT, computed tomography; CTPA, computed tomography pulmonary angiogram. *p < .05, statistically significant. Data are expressed as the number and percentage.

Figure 2. Pathological examination image (HE staining). (A) Infiltration of eosinophils and lymphocytes in lung interstitium (magnification: ×200). (B) Pleural tissue shows many eosinophils infiltrated in the fibrous connective tissue (magnification: ×200). (C) Pronounced eosinophil infiltration in bone marrow tissue (magnification: ×200). (D) EOS infiltration is seen in mediastinal lymph nodes (magnification: ×400). (E) EOS infiltration in the skin tissue of the right lower limb (magnification: ×100). (F) EOS in pleural effusion smears (×200). HE, haematoxylin and eosin; EOS, eosinophils.

Table 4. Comparison of pathological examination results between idiopathic HES and parasite HES groups.

|                                | Idiopathic HES group (n = 16) | Parasite HES group (n = 20) | P value |
|--------------------------------|-------------------------------|-----------------------------|---------|
| EOS ratio of bone marrow smear ≥ 20% | 10 (62.5%)                  | 9 (45%)                     | .335    |
| EOS infiltrate in bone marrow biopsy | 12/15 (80%)                  | 6/9 (66.67%)                | .635    |
| Positive EOS in sputum smear   | 0 (0)                         | 1/1 (100%)                  | –       |
| Positive EOS in pleural fluid  | 1/2 (50%)                     | 1/3 (33.33%)                | 1.000   |
| Positive EOS in bronchoalveolar lavage fluid | 2/9 (22.22%)    | 5/11 (45.45%)               | .374    |
| EOS infiltrate lung and pleura | 2/5 (40%)                     | 4/9 (44.44%)                | 1.000   |
| EOS infiltrate lymph nodes     | 1/1 (100%)                    | 0 (0)                       | –       |
| EOS infiltrate skin tissue     | 0 (0)                         | 1/1 (100%)                  | –       |

EOS, eosinophils; idiopathic HES group, patients with HES of an unknown cause; parasite HES group, patients with parasitic infection. *p < .05, statistically significant. Data are expressed as the number and percentage.
16 patients were administered glucocorticoids combined with praziquantel or albendazole (initial dose of prednisone was 10–80 mg/day; the total dose of praziquantel was 150 mg/kg for an average of 3 days, and albendazole was 10–20 mg/kg/day for 7 days). After 1–4 weeks of steroid treatment, symptoms and related indicators were improved, and the differences before and after treatment were statistically significant ($p < .05$) (Table 5). The remaining two patients in the idiopathic HES group (ICS only), and four patients in the parasite HES group (deworming only) were not treated with corticosteroids and had poor responses.

According to the patient’s condition, glucocorticoids were gradually decreased and discontinued, and patients were followed up for 6–12 months. The duration of glucocorticoid therapy in the idiopathic HES group was significantly longer than that in the parasite HES group (4 [2.75–11.5] vs. 2.25 [1–3] months, $p < .05$). The overall prognosis was good, and 81.25% of the patients were clinically cured in the parasite HES group; however, relapse occurred easily in the idiopathic HES group. A comparison of outcomes between the idiopathic HES and parasite HES groups showed a significant difference in prognosis between the two groups ($p < .05$) (Table 6).

**Discussion**

HES results in continuously elevated EOS infiltration into systemic tissues, causing inflammatory damage and associated complex clinical features. Involvement of the respiratory system is characterised by common symptoms as well as obvious AHR, such as paroxysmal cough or wheezing (asthma-like symptoms). There is little evidence on the association between asthma and HES [8]; therefore, it is easy to ignore the

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**Table 5.** Comparison of laboratory examination and pulmonary function before and after treatment.

|                          | Pretherapy          | Post-treatment        | $P$ value |
|--------------------------|---------------------|-----------------------|-----------|
| **Idiopathic HES group** |                     |                       |           |
| White blood cell (10^9/L) | 10.62 (7.19–17.18)  | 12.22 (8.89–15.44)    | 1.000     |
| Eosinophil (10^9/L)      | 2.37 (1.85–5.01)    | 0.39 (0.07–0.95)      | .002*     |
| Arterial oxygen pressure (mmHg)$^b$ | 68.75 (63.30–84.50) | 93.65 (74.43–106.00) | .031*     |
| Arterial carbon dioxide partial pressure (mmHg)$^a$ | 32.5 (31.25–40.13) | 36.9 (34.18–39.18) | .687     |
| FEV1 (%)$^b$            | 38.40 (28.1–67.90)  | 63.80 (48.80–91.60)   | .016*     |
| FVC (%)$^b$             | 61.70 (39.60–83.30) | 87.00 (76.60–100.70)  | .016*     |
| FEV1/FVC (%)$^b$        | 68.94 (52.04–79.42) | 71.50 (61.60–77.67)   | .453      |
| **Parasite HES group**  |                     |                       |           |
| White blood cell (10^9/L) | 9.59 (7.5–18.81)    | 9.31 (7.58–13.48)     | .804      |
| Eosinophil (10^9/L)      | 2.02 (1.81–5.48)    | 0.62 (0.18–0.96)      | .001*     |
| Partial pressure of oxygen (mmHg)$^c$ | 66.4 (64.5–68.3)    | 75.7 (70.4–81)        | –         |
| Partial pressure of carbon dioxide (mmHg)$^c$ | 39.1 (44.6–33.6)    | 43.45 (48.7–38.2)     | –         |
| FEV1 (%)$^d$            | 50.40 (36.35–67.10) | 80.50 (73.50–99.0)    | .039*     |
| FVC (%)$^d$             | 76.90 (68.95–87.55) | 101.00 (90.15–109.80) | .180      |
| FEV1/FVC (%)$^d$        | 53.90 (42.90–63.03) | 69.7 (58.35–79.85)    | .289      |

$n = 6; ^a n = 7; ^b n = 2; ^c n = 9$. Data are expressed as median (interquartile range).

**Table 6.** Comparison of glucocorticoid use time and outcome between idiopathic HES and parasite HES groups.

|                          | Idiopathic HES group (n = 14) | Parasite HES group (n = 16) | $P$ value |
|--------------------------|--------------------------------|----------------------------|-----------|
| Duration of glucocorticoid use (M) | 4 (2.75–11.5) | 2.25 (1–3) | .007*     |
| Clinical cure            | 5 (35.71%)                     | 13 (81.25%) | .024*     |
| No recurrence            | 2 (40%)                        | 12 (92.31%) | .044*     |
| Recrudescence            | 3 (60%)                        | 1 (7.69%) | .044*     |
| Re-clinical cure         | 1 (33.33%)                     | 0 (0)        | 1.000     |
| Re-improvement           | 1 (33.33%)                     | 1 (100%)     | 1.000     |
| Re-under treatment       | 1 (33.33%)                     | 0 (0)        | 1.000     |
| Improvement              | 9 (64.29%)                     | 2 (12.5%) | .007*     |
| Death                    | 0 (0)                           | 1 (6.25%) | 1.000     |

*p < .05, statistically significant. Data are expressed as the number and percentage or median (interquartile range). Clinical cure: the symptoms and signs of the patient disappeared, there is no abnormality in laboratory and imaging examination, the standard of drug withdrawal was reached and the drug stopped, and there was a follow-up for 6–12 months without relapse; recurrence: the recurrence of the same or similar clinical manifestations during the follow-up after drug withdrawal; improvement: the condition is relieved after treatment, the laboratory and imaging examinations are better than before, and the drug dose has been gradually reduced but did not meet the drug withdrawal standard; the patient did not return to the hospital as required in the follow-up stage; death: the cause of death was attributed to hypereosinophilic syndrome.

Idiopathic HES group, patients with HES of an unknown cause; parasite HES group, patients with parasitic infection (steroid combined with deworming therapy for 1–4 weeks).
manifestations of extrapulmonary involvement and misdiagnose eosinophilic pneumonia or bronchial asthma due to prolonged wheezing symptoms. Patients with paroxysmal wheezing or cough who were diagnosed with numerous acute attacks of bronchial asthma were finally diagnosed with HES of different causes [9–12], suggesting that asthma-like symptoms may be a prominent manifestation in some HES patients. When there is mild or no involvement of the extrapulmonary organs, the clinical manifestations are minor, and hospitalisation temporarily partially relieves the symptoms, it is easy to erroneously diagnose such patients with bronchial asthma. This can worsen the disease and delay treatment which, in severe cases, can lead to multiple organ failure or even death [13]. Therefore, it is pertinent to summarise the clinical characteristics of HES initially presenting with asthma-like symptoms, and analyse the characteristics and treatment of idiopathic and parasitic HES, to improve clinician understanding of the disease.

The most common cause of secondary HES is parasitic infection (predominantly male) [1,14]. In this study, the male-to-female ratio in the parasite HES group was 17:3, which may be related to male social activities and an unclean diet; however, the male-to-female ratio of idiopathic HES group patients was 1:1, which is consistent with the literature [15]. Among both groups, 74.19% of patients had an abnormal pulmonary function, of whom eight were positive for BDT. The remaining eight patients with normal pulmonary function were examined only after their wheezing symptoms were relieved. It is suggested that abnormal lung function due to pulmonary involvement from idiopathic or parasitic HES is reversible. Our research shows that there was no significant difference in the clinical manifestations, laboratory test results, and pulmonary function between the two groups; therefore, it is difficult to distinguish between parasite HES and idiopathic HES based on the aforementioned manifestations, which also appear very similar to those of bronchial asthma. In addition to an EOS count $>1.5 \times 10^{9}/L$, multiple organ dysfunction is also a major feature of HES. In this study, a rash, abnormal colour ultrasound, thrombosis, lymph node enlargement, chest CT, and abnormal pathological manifestations suggested that the blood, lungs, heart, gastrointestinal tract, lymph nodes, and skin were involved. Of course, malignant tumours and autoimmune diseases were excluded. The exclusion of secondary factors is the first step in the HES diagnostic process, and comprehensive personal history data collection and repeated parasitic testing are the keys for screening for parasitic infections.

Our study showed that bronchial asthma, pulmonary infection, and COPD were the most common misdiagnosed diseases; the experience of medical treatment in the idiopathic HES and parasite HES groups was similar, and there was no significant difference in the median time from the onset of symptoms to diagnosis. With asthma-like manifestations as the first symptom, obstructive ventilation dysfunction is completely reversible or irreversible and should be distinguished from bronchial asthma or refractory asthma. The eosinophil count in the peripheral blood of asthma was far less than $1.5 \times 10^{9}/L$, without other organ infiltrates and ICS with good effect [16–18]. Therefore, persistently elevated levels of EOS, bone marrow infiltration of EOS, and systemic damage cannot be explained by asthma, as is crucial to make the final diagnosis. Middle-aged and elderly men with a long history of smoking have recurrent wheezing and obstructive ventilatory dysfunction, which should be distinguished from COPD. Pulmonary exudation can also be observed when acute exacerbation of COPD is complicated with infection but can be absorbed after anti-infection. Although the symptoms can be relieved after systemic steroid treatment, the pulmonary function cannot return to normal, which is obviously different from that in patients in our study. ABPA can also cause similar manifestations, due to the allergic reaction induced by Aspergillus spores inhaled into the respiratory tract, but ABPA does not cause EOS infiltration into the bone marrow, and the total serum IgE level is $>1,000$ IU/mL. Pulmonary imaging also shows characteristic lesions (tree bud sign, mucus thrombus, and central bronchiectasis) and Aspergillus can be cultured in BALF. When asthma-like symptoms are poorly controlled, it is necessary to determine whether other systems are damaged. Symptoms of EGPA (prodromal phase and/or infiltration of EOS phase) are also similar to those of HES observed in our study. It can also involve multiple systems, which makes it difficult to distinguish clinically. When the lungs were involved, the chest CT also showed ground-glass exudation, consolidation, and nodules. However, EGPA is essentially vasculitis. When it develops into vasculitis, there are obvious systemic symptoms such as fever, weight loss, fatigue, abnormal inflammatory and immune indices, positive autoantibodies including anti-neutrophil cytoplasmic antibody, and histopathological changes (small vessel necrotising vasculitis and granuloma accompanied by infiltration of EOS in surrounding tissues), which are important for the diagnosis of EGPA.
In our study, all cases were negative for autoantibodies and showed no vasculitis or granuloma on histopathological examination, which was the key for excluding EGPA.

The underlying mechanism of wheezing caused by HES remains unclear. Studies have shown that EOS cationic protein and peroxidase released by EOS can destroy the integrity of the bronchial epithelium; induce the release of histamines by mast cells; and cause bronchial contraction, edema, and airway remodelling [4]. In this study, many EOS and lymphocytes infiltrated the alveolar interstitium, and EOS were found in BALF and sputum smears, suggesting that EOS aggregate, activate, and release inflammatory mediators in the bronchial and pulmonary interstitium, leading to AHR. After treatment, the EOS count was decreased and wheezing symptoms disappeared in both groups, suggesting that chronic inflammation induced by EOS in the respiratory tract may be the cause of asthma-like symptoms in HES. In addition, degranulation of EOS and release of a variety of mediators can stimulate platelet activation and aggregation, and damage vascular endothelial cells, both of which promote thrombosis. The tissue factor stored by EOS is the main initiator of blood clotting [19–21]; therefore, thrombosis is the main manifestation of HES involving blood vessels [22–24]. In the idiopathic HES group, three patients had pulmonary artery involvement and two had peripheral vein involvement, which was misdiagnosed as simple thromboembolism. The anticoagulant effect is poor and life-threatening in severe cases. These characteristics suggest that clinicians should pay attention to the EOS count in patients with pulmonary or other vascular embolisms, especially in those with a recurrent embolism or poor anticoagulant response.

Regardless of the cause of HES, the purpose of therapy is to reduce the EOS count and EOS-mediated organ dysfunction. The main therapeutic options for HES patients can be divided into five groups: corticosteroids; cytotoxic agents; tyrosine kinase inhibitors (TKIs); monoclonal antibodies; and chemotherapy [25]. Corticosteroids can be used as first-line therapy in patients with strictly defined HES, and the recommended dose is prednisone 1 mg/kg/day [26]. With the control of symptoms and a decrease in EOS count <1.5 × 10⁹/L, the dose of prednisone can be gradually reduced [27]. However, secondary HES should be treated according to the primary aetiology, and individualised treatment should be provided for vital organ involvement. A combination of corticosteroids is recommended, starting with prednisone at 1 mg/kg/day [28]. In this study, the treatment efficacy in patients in both groups was significant. After 1–4 weeks of treatment, symptoms were relieved or disappeared, EOS count decreased, lung function recovered, and the differences before and after treatment were statistically significant. The duration of steroid therapy in the idiopathic HES group was significantly longer than that in the parasite HES group. The prognosis of the parasite HES group was good, and 81.25% of the patients were successfully treated. Among them, one patient had a deteriorated condition and subsequently died during the maintenance of steroid reduction, suggesting that the injury caused by a parasitic infection should not be ignored. The allergic state of the body is activated, and reexposure to allergens is likely to lead to recurrence or deterioration. In the idiopathic HES group, it is easy to relapse, and steroid therapy is lengthy. Nine patients did not return to the hospital during the period of steroid reduction after disease control; therefore, the median time of steroid therapy should be longer.

Repeated symptoms, signs of organ damage, and/or a significant increase in EOS at prednisone >10 mg/day indicate that treatment should be combined with other immunosuppressive therapies [27]. Hydroxyurea can be used as a first-line drug or in combination in steroid-insensitive patients, while interferon-α is usually used as a second-line agent after steroid treatment failure [26]. In recent years, TKIs have been applied to treat HES, which mainly depends on the aetiology and subtype and has strict indications. For example, imatinib is considered a definitive treatment for patients with HES in myeloid neoplasms (usually MDS/MPNs) and FIP1L1-PDGFRA rearrangement or PDGFRA/B-rearranged neoplasms [29]. Imatinib was chosen when idiopathic HES did not respond or was not applicable to corticosteroids therapy [30]. Fortunately, our patient showed a good response to corticosteroids therapy. In addition, case reports have found that alemtuzumab (anti-CD52 monoclonal antibody) had a certain effect on refractory HES [31]. In addition, anti-IL-5 and anti-IL-5 receptors for HES treatment are still in the research stage, and several drugs have reached phase 2 and phase 3 trials [26]. Idiopathic HES is not only an exclusive but also a temporary diagnosis. It has been reported that patients developed hematological malignant tumours 10 years later [32]. For patients who are still prone to recurrent or severe systemic damage after therapy, long-term follow-up and regular review of autoantibodies is required. Based on the experience of this study, a diagnostic flowchart for asthma-like symptoms is...
presented, which may help reduce misdiagnosis (Figure 3).

**Conclusions**

In summary, asthma-like symptoms, obstructive ventilatory disorder or positive BDT, and poor response to ICS are not necessarily indicative of refractory asthma; patients with EOS count $>1.5 \times 10^9/L$ should be considered for the possibility of HES. The clinical characteristics of HES of different aetiologies are similar. Systemic corticosteroid therapy is preferred for both idiopathic and parasitic infections, the latter requiring combined deinsectization and showing good clinical efficacy. Idiopathic HES is treated with prolonged corticosteroids and relapses easily.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**Author contributions**

XW, XL, and ZW participated in the patients’ clinical management and wrote the draft of the manuscript. HZ, JD, and SX collated the images for analysis. JZ was responsible for critical revision of the manuscript. All authors have reviewed and approved the final version of the manuscript.
Funding
This work was supported by the Natural Science Foundation of China under Grants NSFC81760010 and 82060364; and the Science and Technology Department of Guangxi Zhuang Autonomous Foundation of Guangxi Key Research and Development Program under Grant GuikeAB20238025.

Data availability statement
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

References
[1] Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol. 2012;130(3):607–612.
[2] Sunagawa K, Nishio H, Kinukawa N, et al. An autopsy case of disseminated strongyloidiasis combined with cytomegalovirus infection. Jpn J Infect Dis. 2011;64(2):150–152.
[3] Mocumbi AO, Goncalves C, Damasceno A, et al. Active schistosomiasis, severe hypereosinophilia and rapid progression of chronic endocardial fibrosis. Cardiovasc J Afr. 2016;27(5):e4–e6.
[4] Woolnough K, Wardlaw AJ. Eosinophilia in pulmonary disorders. Immunol Allergy Clin North Am. 2015;35(3):477–492.
[5] Lima Álvarez J, Peña Gríñan N, Simón Pilo I. Eosinophilic pleural effusion as a manifestation of idiopathic hypereosinophilic syndrome. Arch Bronconeumol. 2016;52(10):538.
[6] Krenke R, Nasilowski J, Korczynski P, et al. Incidence and aetiology of eosinophilic pleural effusion. Eur Respir J. 2009;34(5):1111–1117.
[7] Papakosta D, Manika K, Kyriazis G, et al. Bronchoalveolar lavage fluid eosinophils are correlated to natural killer cells in eosinophilic pneumonia. Respir. 2009;78(2):177–184.
[8] Spry CJ, Davies J, Tai PC, et al. Clinical features of fifteen patients with the hypereosinophilic syndrome. Q J Med. 1983;52(205):1–22.
[9] Khan WA, Santhanakrishnan K. Hypereosinophilic syndrome secondary to strongyloides infection: a case of recurrent asthma exacerbations. BMJ Case Rep. 2013;2013(1):bcr2013009587–bcr2013009587.
[10] Karnak D, Kayacan O, Beder S, et al. Hypereosinophilic syndrome with pulmonary and cardiac involvement in a patient with asthma. CMAJ. 2003;168:172–175.
[11] Lim KS, Ko J, Lee SS, Shin B, et al. A case of idiopathic hypereosinophilic syndrome presenting with acute respiratory distress syndrome. Allergy Asthma Immunol Res. 2014;6(1):98–101.
[12] Xie J, Zhang J, Zhang X, et al. Cough in hypereosinophilic syndrome: case report and literature review. BMC Pulmon Med. 2020;20:1–9.
[13] Wu P, Chen Y, Zhang H, et al. Idiopathic hypereosinophilic syndrome presenting with multiple organ damage: a case report. Medicine. 2019;98(10):e14532.
[14] Hwang KJ, Heo SH, Chang DI. Multiple microembolic brain infarctions in Clonorchis sinensis infestation. J Neurol Sci. 2012;319(1–2):133–134.
[15] Dulovery MM, Patel RR, Schneider F, et al. Lung involvement in hypereosinophilic syndromes. Respir Med. 2011;105(1):114–121.
[16] Håkansson KEJ, Rasmussen LHJ, Godtfredsen NS, et al. The biomarkers suPAR and blood eosinophils are associated with hospital readmissions and mortality in asthma – a retrospective cohort study. Respir Res. 2019;20(1):258.
[17] Lababidi HM, AlSowayigh OM, BinHowemel SF, et al. Refractory asthma phenotyping based on immunoglobulin E levels and eosinophilic counts: a real life study. Respir Med. 2019;158:55–58.
[18] Wijnant SRA, Lahousse L, De Buyzere ML, et al. Prevalence of asthma and COPD AND blood eosinophil count in a Middle-aged belgian population. JCM. 2019;8(8):1122.doi:10.3390/jcm8081122.
[19] Wang JG, Mahmud SA, Thompson JA, et al. The principal eosinophil peroxidase product, HOSCN, is a uniquely potent phagocyte oxidant inducer of endothelial cell tissue factor activity: a potential mechanism for thrombosis in eosinophilic inflammatory states. Blood. 2006;107(2):558–565.
[20] Moosbauer C, Morgenstern E, Cuvelier SL, et al. Eosinophils are a major intravascular location for tissue factor storage and exposure. Blood. 2007;109(3):995–1002.
[21] Cugno M, Marzano AV, Lorini M, et al. Enhanced tissue factor expression by blood eosinophils from patients with hypereosinophilia: a possible link with thrombosis. PLOS One. 2014;9(11):e111862.
[22] Li D, Xu L, Lin D, et al. Acute pulmonary embolism and deep vein thrombosis secondary to idiopathic hypereosinophilic syndrome. Respir Med Case Rep. 2018;25:213–215.
[23] Todd S, Hemmaway C, Nagy Z. Catastrophic thrombosis in idiopathic hypereosinophilic syndrome. Br J Haematol. 2014;165(4):425.
[24] Chen TS, Xing LH, Wang SL, et al. Pulmonary embolism and deep vein thrombosis in patients with hypereosinophilic syndrome. Blood Coagul Fibrinolysis. 2016;27(7):831–834.
[25] Dispenza MC, Bochner BS. Diagnosis and novel approaches to the treatment of hypereosinophilic syndromes. Curr Hematol Malig Rep. 2018;13(3):191–201.
[26] Stella S, Massimino M, Manzella L, et al. Molecular pathogenesis and treatment perspectives for hypereosinophilia and hypereosinophilic syndromes. JMS. 2020;22(2):486.
[27] Shomali W, Gotlib J. World health organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. Am J Hematol. 2019;94(10):1149–1167.
[28] Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and...
response to therapy. J Allergy Clin Immunol. 2009;124(6):1319–1325.

[29] Helbig G. Imatinib for the treatment of hypereosinophilic syndromes. Expert Rev Clin Immunol. 2018;14(2):163–170.

[30] Hana CK, Caldera H. Hypereosinophilic syndrome, multiorgan involvement and response to imatinib. Cureus. 2020;12(6):e8493.

[31] Verstovsek S, Tefferi A, Kantarjian H, et al. Alemtuzumab therapy for hypereosinophilic syndrome and chronic eosinophilic leukemia. Clin Cancer Res. 2009;15(1):368–373.

[32] Jin JJ, Butterfield JH, Weiler CR. Hematologic malignancies identified in patients with hypereosinophilia and hypereosinophilic syndromes. J Allergy Clin Immunol Pract. 2015;3(6):920–925.