

# Diagnostic procedure for idiopathic eosinophilic pleural effusion: A single-center experience

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## Research article

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## Abstract

**Background:** Eosinophilic pleural effusion (EPE) is attributed to many known and obvious causes, but some patients remain idiopathic even after thorough clinical work-up. The present study aims to better characterize idiopathic EPE (IEPE) and to outline the diagnostic procedure for this disease.

**Methods:** The complete clinical data of eleven prospectively collected consecutive patients with IEPE were analysed and preliminary diagnostic procedure of IEPE in our hospital was performed.

**Results:** All the 11 patients had respiratory symptoms and unilateral pleural effusion (PE) occurred in 4 patients. The mean percentage of eosinophils in PE was 22.4% (range, 12.4%-50.5%). Lactate dehydrogenase, adenosine deaminase, protein and carcinoembryonic antigen in PE were 246.0 U/L (range, 89.8-421.9 U/L), 13.8 U/L (range, 1.8-24.0 U/L), 42.6 g/dl (range, 32.8-52.6 g/dl) and 2.17 mg/mL (range, 0.46-4.31 mg/mL), respectively. A parasite-specific IgG antibody in blood and parasite eggs in stool were negative. No evidence of tuberculosis or malignancy was observed in pleural biopsy. Symptoms and abnormal pulmonary imaging were eliminated after glucocorticoid use.

**Conclusions:** IEPE is a diagnosis of exclusion. Patients with EPE without a clear cause should be asked for complete medical, surgical and drug-related history, and we recommend a thorough work-up and follow-up after the use of glucocorticoid until the effusion does not reappear.

## Background

Eosinophilic pleural effusion (EPE) contains at least 10% eosinophils of white cell differential count in pleural fluid <sup>[1-2]</sup>, accounting for 5% to 16% of the total exudative pleural effusions. Many known and obvious causes attribute to EPE such as trauma, infectious diseases, malignant tumours, asbestos exposure and several medications <sup>[1-5]</sup>. However, approximately 14%–25% of patients with EPE are idiopathic even after thorough clinical work-up and such cases without specific etiology are considered as idiopathic EPE (IEPE), and likely benefit from the use of glucocorticoids <sup>[4-6]</sup>.

The reported prevalence of IEPE is not inconsistent. 35% of patients with EPE without apparent causes were found in Adelman's study <sup>[1]</sup>, but this number was only 8.5% in another study <sup>[6]</sup>. A meta-analysis and systematic review <sup>[4]</sup> concluded that the most two common causes of EPE are malignancy (26%) and IEPE (25%). Compared with non-EPE, EPE was more likely to be idiopathic.

Although IEPE has been regarded as an important cause of EPE, few prospective studies are available <sup>[7-11]</sup>. The clinical characteristics and diagnostic approach for IEPE remain not quite clear to physicians. Delayed diagnosis or misdiagnosis probably leads to significant morbidity and even mortality. To better characterize IEPE and to outline its diagnostic procedure, in the present study, we prospectively collected and analysed the complete clinical data of eleven consecutive patients with EPE. Importantly, a preliminary diagnostic procedure of IEPE was provided.

## Methods

### *Patients*

Five hundred and fifty-six consecutive patients with pleural effusion (PE) were admitted to the First Affiliated Hospital of Guangzhou Medical University due to respiratory symptoms between January 2016 and January 2018. Four hundred and eighty-two patients with pleural effusion or pleural pulmonary involvement scanned by chest high-resolution computed tomography (HRCT) and those with eosinophils less than 10% in pleural effusion were excluded from this study. A total of 74 patients with EPE were asked for past medical, surgical, traumatic infectious and drug-related history and then received extensive work-up for definite EPE etiology. Finally, the complete clinical data of 11 patients with IEPE prospectively were collected and analysed. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University.

### *Exclusive diagnosis*

The common etiology of EPE including malignant PE (MPE), tubercular PE (TPE), parapneumonic PE (PPE) and pleural parasitic infestation (PPI) were excluded by laboratory tests.

## Results

### *Characteristics of patients with IEPE*

Before laboratory tests and imaging examination for EPE, it is necessary to review patients past medical and surgical history to identify a primary treatable cause. Additionally, review of the drug intake, occupational and infectious disease exposure and comorbid conditions to rule out the common causes of EPE. Totally, the complete clinical data of 11 patients with IEPE were finally collected and analysed in this study. The clinical characteristics of 11 cases were summarized in Table 1. Three were 5 male and 6 female patients with a median age of 49.8 years (range, 30–67 years). All cases had respiratory symptoms including shortness of breath (n = 10), cough (n = 3), chest pain (n = 3), fever (n = 3) and excessive sputum (n = 1). The duration of these symptoms ranged from 15 days to more than 2.5 months. Pulmonary physical examination revealed remarkably decreased breath sounds with dullness to percussion on the lateral or bilateral chests, without other significantly positive signs. The diagnosis was similar to PPE in 3 cases, five cases were initially misdiagnosed with TPE. A patient was considered as MPE and another one was misdiagnosed with chronic heart failure (CHF).

### *Laboratory tests for peripheral blood cell (PBC) and serological examination*

PBC analysis was conducted in all patients (Table 2). Leukocytosis of peripheral blood ( $>1010^9/L$ ) was observed in 4 cases (case 2, 3, 7 and 11), and eosinophilia ( $>0.510^9/L$ ) was seen in 5 cases (case 2, 3, 5, 7 and 11). Moreover, no specific findings were observed in blood tests, including liver function panel, thyroid function test, C-reactive protein, erythrocyte sedimentation rate, and interferon- $\gamma$  release assays (IGRAs), carcinoembryonic antigen (CEA) and brain natriuretic peptide (BNP). Antinuclear antibody, rheumatoid factor antibody, proteinase 3, myeloperoxidase and anticyclic citrullinated peptide antibody were not detected. Sputum smears and cultures for fungi, acid-fast bacilli and other bacteria were also negative. Parasite-specific IgG antibody showed a negative result, and parasite eggs in stool were not determined.

### *Invasive work-up*

After thoracentesis and pleura biopsy, pleural effusions were collected for further analysis. Bloody effusions (due to thoracic trauma or surgery) and effusions associated with air in the pleural space were not found in this study. Bilateral effusions were seen in 7 patients. Four cases had intrapulmonary involvement and intrapulmonary lesions presented as consolidation or infiltration. Bronchoscopy and transbronchial lung biopsy (TBLB) were performed in these patients, but eosinophilic infiltration was not found, without any evidence of tuberculosis or malignancy. Furthermore, two cases developed pericardial effusion as detected by chest CT (Figure 1A and 1B).

### *Eosinophils and other pleural parameters in pleural fluid*

Pleural samples were acquired by combined ultrasound-guided cutting needle biopsy and standard pleural biopsy<sup>[12]</sup>. EPE was detected in all patients, and the mean percentage of eosinophils in pleural effusion was up to 22.4% (range, 12.4%–50.5%). The mean concentrations of pleural effusion lactate dehydrogenase (LDH), adenosine deaminase (ADA), protein, CEA and BNP were 246.0 U/L (range, 89.8–421.9 U/L), 13.8 U/L (range, 1.8–24.0 U/L), 42.6 g/dl (range, 32.8–52.6 g/dl) and 2.17 mg/mL (range, 0.46–4.31 mg/mL), and 1217.58 (range, 35.24–432.2 mg/mL), respectively (Table 3). Pleural effusion tuberculosis-DNA (TB-DNA), acid-fast bacilli smears and pleural effusion culture for fungi or bacteria were negative. Eosinophilic infiltration, lymphocyte infiltration, granulocytic infiltration and noncaseating granulomas were found in the pleural samples, but no evidence of either tuberculosis or malignancy was found in any of these patients.

Additionally, comprehensive haematological detection was performed in case 2 and 11. Smear and biopsy of bone marrow showed no evidence of hypereosinophilia and infiltration via lymphoproliferative malignancy. The possibility of myeloproliferative hypereosinophilic syndrome was excluded by negative FIP1L1-PDGFRA and BCR-ABL gene transcriptions. In case 3 and 10, positron emission tomography/computed tomography (PET/CT) was used as a systemic search to reveal that the lungs and pericardium were involved, except for pleural effusion.

### *Exploratory treatment and follow-up*

After the initial diagnosis of IEPE, patients were tried to treat with glucocorticoid (initial dose of prednisone: 1 mg/kg of body weight per day). If glucocorticoid resolved symptoms and abnormal pleural pulmonary radiographic signs, consecutive reduction of 10 mg per month was made. Physical examination with chest radiography, ultrasound and/or CT were followed up after the use of glucocorticoid.

The median follow-up was 14.4 months (range, 8–16 months). All the patients showed total regression of the pleural effusion, without re-occurrence. These patients remained stable during follow-up and did not receive any additional therapy. Figure 2 showed the follow-up chest CT of a patient (case 3).

### *Preliminary diagnostic procedure of IEPE*

IEPE is a diagnosis of exclusion. Patients with EPE without a clear cause should be asked for complete medical and surgical history, and we recommend a follow-up after the use of glucocorticoid until the effusion resolves or a known cause becomes apparent. A preliminary diagnostic procedure of IEPE was summarized and shown in Figure 3.

## **Discussion**

EPEs account for 5% to 16% of the exudative pleural effusions, and IEPE is an important cause of EPEs which can almost always be treated medically [4, 5]. However, limited well-documented cases have been described [7–11]. In this study, we tried to analyse clinical characteristics of IEPE and to make diagnostic procedure clear.

Archontogeorgis K et al. [13] firstly investigated the diagnostic approach in 10 patients with IEPE, but the clinical characteristics of IEPE was not assessed. We tried to describe the clinical features of IEPE in spite of 11 cases prospectively collected. Shortness of breath is one of major symptoms; Moreover, fever, productive cough, fatigue, lymphadenopathy, splenomegaly and ascites often exist [4, 5]. Most patients had bilateral pleural effusion [7–9, 11], but some had just unilateral effusion [10]. We found all the 11 patients developed respiratory symptoms which were similar to IEPE symptoms. Among these cases, 7 had bilateral effusion and 4 had lung involvement. Previous reports [7–11] showed eosinophils seemed always significantly elevated, reaching up to  $3.5 \times 10^9/L$ . But the number of eosinophils were normal or slightly elevated. Due to its nonspecific characteristics and laboratory tests, some patients were initially misdiagnosed.

Current investigations on pleural effusions emphasise the use of a diagnostic algorithm or recommend the use of a stepwise approach [14–17]. Thoracocentesis was performed to ascertain the nature of pleural effusion and to differentiate it from other conditions.

Consistent with the results of a previous study [13], pleural effusions in the 11 patients were exudative according to Light's criteria. Pleural CEA, ADA and LDH were nonspecific in these 11 cases. Prospective studies with more patients need be conducted to evaluate the diagnostic value of such effusion parameters.

A meta-analysis concluded that the most common cause of EPEs is malignancy (26%) [4]. Therefore, malignancy must be excluded for IEPE diagnosis. CEA, as a tumour marker, plays a role in MPE differentiation. Pleural CEA is often positive in suspected patients with malignancy [18, 19]. In this study, CEA in the serum and pleural effusion were at normal level ( $<5 \text{ mg/mL}$ ). Pleura biopsies seem to be mandatory when malignancy is excluded. Archontogeorgis K et al. [13] emphasised that pleuroscopy is mandatory in diagnosing IEPE. In this study, pleural samples were collected by using combined ultrasound-guided cutting needle biopsy and standard pleural biopsy, without thoracoscopic assessment. Enough and pleura biopsies were obtained, and the sensitivity and accuracy reached up to 88.6% and 93.8%, respectively [12], which were close to thoracoscopy examination [20]. Eosinophilic infiltration was found in 6 cases. However, there were no evidence of tuberculosis or malignancy in these patients.

Except for malignancy, the causes of EPE vary and complicated, including parapneumonic effusions, pleural air/blood, tuberculosis, transudate, and collagen vascular disease [4, 5]. Therefore, a thorough work-up is required to rule out known and obvious causes of EPE. We did not identify any related medications, autoimmune disease and chest trauma in these cases. In our previous study [21], we confirmed that in patients with unexplained pleural effusion, parasite-specific IgG antibody detection had to be done when pleural fluid testing showed EPE. Physicians should consider a diagnosis of PPI should be considered when parasite-specific IgG antibody is positive. Based on this, we excluded PPI diagnosis.

Hypereosinophilic syndrome (HES) was redefined in 2010 as more than  $1500/\text{mm}^3$  eosinophils without a discernible secondary cause (eg, HIV infection, parasite or worm infection, allergic diseases, drug allergies, and nonhematologic malignancies) [22]. Idiopathic HES (IHES) sometimes presented with EPE [23], but the causality of IHES and EPE was not reached. Although the absolute eosinophil count was  $2.16 \times 10^9/L$  in case 2, IHES diagnosis was excluded after comprehensive haematological determinations. Echocardiography displayed pericardial effusion in a case, while lung involvement was shown in 4 cases. So, we think PET/CT or transbronchial lung

biopsy to verify the diagnosis of chronic eosinophilic pneumonia in lung involvement needs confirmation. When EPE has with no apparent etiology, the diagnosis of IEPE should be considered.

This study had limitations. Because this is a single-center experience with a small number of patients was quite small, the characteristics IEPE were not well defined. A large, multicentre, prospective study is needed for validation of the findings.

## Conclusions

IEPE is a diagnosis of exclusion. Patients with EPE without a clear cause should be asked for complete medical, surgical and drug-related history, and we recommend a thorough work-up and follow-up after the use of glucocorticoid until the effusion does not reappear.

## Abbreviations

EPE: eosinophilic pleural effusion; IEPE: idiopathic EPE; PE: pleural effusion; HRCT: high-resolution computed tomography; MPE: malignant PE; TPE: tubercular PE; PPE: parapneumonic PE; PPI: pleural parasitic infestation; CHF: chronic heart failure; PBC: peripheral blood cell; IGRAs:interferon- $\gamma$  release assays; CEA: carcinoembryonic antigen; BNP: brain natriuretic peptide; TBLB: bronchoscopy and transbronchial lung biopsy; LDH: lactate dehydrogenase; ADA: adenosine deaminase; TB-DNA: tuberculosis-DNA; PET/CT: positron emission tomography/computed tomography; HES: hypereosinophilic syndrome; IHES: idiopathic HES.

## Declarations

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### *Authors' contributions*

Study concept and design: JW and JH. Acquisition of data: JW, WL, YZ and PS. Statistical analysis and interpretation of data: JW and YZ. Drafting of the manuscript: JW, WL and YZ. Critical review/revision of the manuscript and approval of the final version: All authors.

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### *Availability of data and materials*

The datasets supporting the conclusions of this article are included within the article and its figures and tables. Additional data may be available from the corresponding author upon reasonable request.

### *Ethics approval and consent to participate*

The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. A written informed consent was obtained from each participant.

### *Consent for publication*

All patients provide written informed consent at recruitment.

### *Competing interests*

None.

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## Tables

**Table 1** Demographic characteristics of eleven patients with IEPE

No	Age(y)/Sex	Chief complaint (duration)	Misdiagnosis	Side of PE	Pathology of pleura biopsy	Treatment	Follow-up (mth)	Other organ involvement
1	56/F	Fever, shortness of breath (20 d)	TPE	Bilateral	Eosinophilic infiltration	Glucocorticoid	9	lung
2	34/M	shortness of breath (2 mth)	N	Right	Eosinophilic infiltration	Glucocorticoid	15	N
3	44/M	Chest pain, shortness of breath (1 mth)	PPE	Bilateral	Lymphocytic infiltration	Glucocorticoid	12	Lung pericardium
4	37/F	Cough, shortness of breath (1 mth)	TPE	Bilateral	Noncaseating granulomas	Glucocorticoid	8	N
5	66/M	Shortness of breath (2.5 mth)	TPE	Bilateral	Lymphocytes infiltration	Glucocorticoid	16	N
6	67/F	Chest pain, shortness of breath (1 mth)	MPE	Left	Eosinophilic infiltration	Glucocorticoid	11	Lung
7	61/M	Cough, excessive sputum, shortness of breath (1 mth)	CHF	Bilateral	Eosinophilic infiltration	Glucocorticoid	10	N
8	55/F	Fever, shortness of breath (1 mth)	TPE	Left	Lymphocytic infiltration	Glucocorticoid	12	N
9	46/F	Cough, chest pain, shortness of breath (2 mth)	PPE	Bilateral	Eosinophilic lymphocytic infiltration	& Glucocorticoid	11	Pericardium
10	52/M	Fever, cough (15 d)	PPE	Bilateral	Granulocytic lymphocytic infiltration	& Glucocorticoid	10	Lung
11	30/F	Shortness of breath (2 m)	TPE	Right	Eosinophilic infiltration	Glucocorticoid	11	N

*Abbreviations:* IEPE, idiopathic eosinophilic pleural effusion; F, female; d, day; TPE, tuberculosis pleural effusion; M, male; mth, month; N, none; PPE, parapneumonic pleural effusion; MPE, malignant pleural effusion; CHF, chronic heart failure.

**Table 2** Blood examinations of the eleven patients with IEPE

No	WBC ( $\times 10^9/L$ )	Eos ( $\times 10^9/L$ )	CEA (ng/mL)	LDH (U/L)	BNP (pg/mL)	ANA (U/mL)	PR3 (U/mL)	MPO (U/mL)	ESR (mm/h)	IGRAs	IgE (U/mL)	Parasite-specific IgG antibodies	Parasite eggs from stool
1	3.21	0.49	2.86	130	100	4.45	3.47	2.15	100	N	-	N	N
2	13.57	2.16	1.80	178	17.43	5.66	4.87	4.80	35	N	223	N	N
3	11.2	0.6	0.67	164	248.50	5.02	0.47	1.29	66	N	339	N	N
4	4.8	0.36	1.38	146	30.41	2.68	2.14	4.64	25	N	-	N	N
5	3.93	0.71	2.17	182	44.56	11.57	1.95	3.79	43	N	243	N	N
6	4.78	0.49	3.23	201	321.32	3.50	2.43	4.23	47	N	-	N	N
7	11.3	0.64	2.10	143	453.45	4.38	2.56	2.46	56	N	-	N	N
8	4.56	0.35	4.56	203	487.23	3.56	2.45	2.67	46	N	115	N	N
9	8.6	0.42	3.56	189	123.2	4.32	3.43	2.87	54	N	231	N	N
10	8.65	0.34	2.89	212	212.67	5.43	4.23	3.45	34	N	-	N	N
11	10.38	0.84	3.56	156	325	4.21	1.24	2.43	46	N	165	N	N

*Abbreviations:* IEPE, idiopathic eosinophilic pleural effusion; WBC, white blood cell; Eos, eosinophils; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; BNP, brain natriuretic peptide; ANA, antinuclear antibodies; PR3, proteinase 3; MPO, myeloperoxidase; IGRAs, interferon- $\gamma$ -release assays; N, negative.

**Table 3** Pleura effusion examinations and pleura pathology of eleven patients with IEPE

No	Eos (%)	CEA (ng/mL)	ADA (U/L)	LDH (U/L)	Protein (g/dl)	BNP (pg/mL)	TB-DNA	AFB smears	Culture of effusion
1	31	1.89	8.1	265	51.8	96.13	N	N	N
2	20	1.53	7.9	338.5	52.6	47.2	N	N	N
3	22.5	0.46	4	209	49.7	35.24	N	N	N
4	50.5	1.08	23.0	421.9	48.3	394.60	N	N	N
5	14.3	2.01	1.8	89.8	37.5	93.35	N	N	N
6	21	1.48	6.7	221.0	43.2	87.46	N	N	N
7	19	1.67	2.8	189.4	39.8	432.2	N	N	N
8	15.2	4.31	24.0	201.2	35.6	412	N	N	N
9	21.2	3.34	20.0	234.4	43.2	231.1	N	N	N
10	18.9	2.67	17	321.4	34.2	243.1	N	N	N
11	12.4	3.4	19.9	214.5	32.8	321.0	N	N	N

*Abbreviations:* IEPE, idiopathic eosinophilic pleural effusion; Eos, eosinophils; CEA, carcinoembryonic antigen; ADA, adenosine deaminase; LDH, lactate dehydrogenase; BNP, brain natriuretic peptide; N, negative; TB-DNA, tuberculosis DNA; AFB, Acid-fast bacilli.

## Figures

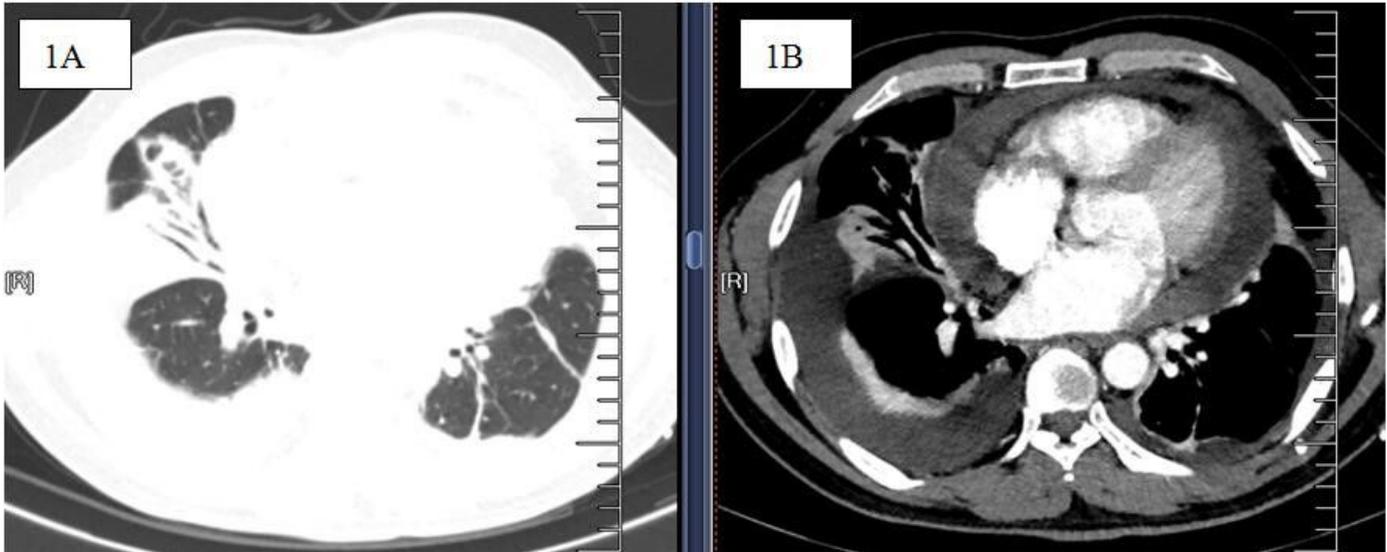


Figure 1

A 44-year-old male patient with IEPE (case 3). Chest CT (A, B) scans showed bilateral pleural effusion and consolidation in the lower right lung, pericardial effusion.

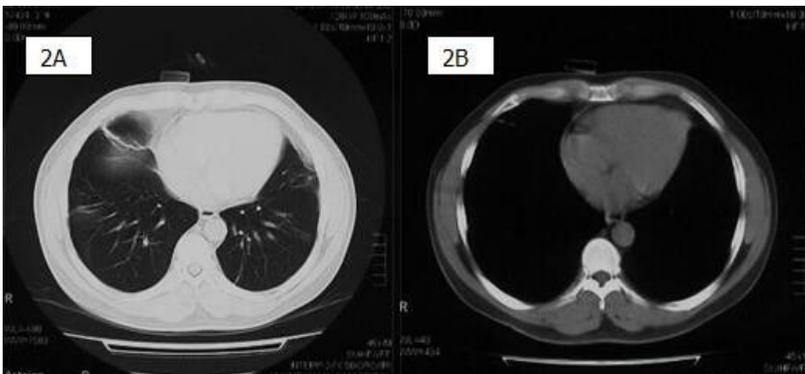
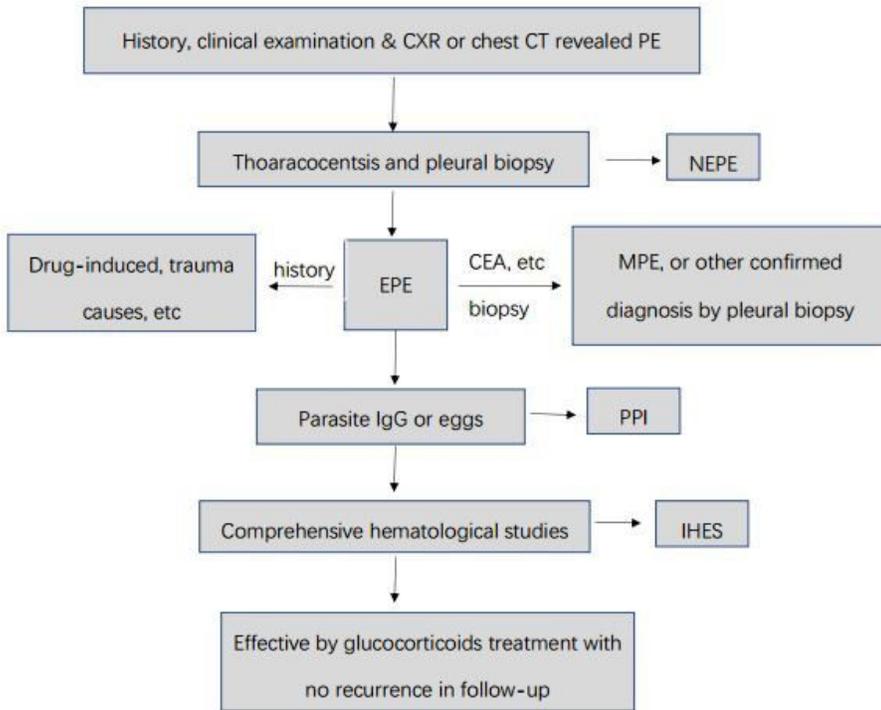


Figure 2

Follow-up chest CT scan of case 3. Total regression of the pleural effusion, consolidation in the lower right lung and pericardial effusion with no recurrences.

## Diagnostic approach for investigation of IEPE



Abbreviations: IEPE, idiopathic eosinophilic effusion; CXR, chest X-ray; PE, pleural effusion; NEPE, non-EPE; CEA, carcinoembryonic antigen; MPE, malignant pleural effusion; PPI, pleural parasitic infestation; IHES, idiopathic hyper eosinophilic syndrome.

**Figure 3**

Schematic diagram of diagnostic procedure of IEPE.