CASE REPORT

A comorbid case of multicentric Castleman's disease and pulmonary hyalinising granuloma successfully treated with tocilizumab and corticosteroid

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SUMMARY

A 49-year-old man with superficial lymphadenopathy presented with symptoms of low-grade fever, general fatigue and weight loss. On examination, multiple superficial lymphadenopathies and brown macules were observed on the trunk. Laboratory studies revealed an elevation of serum C reactive protein and interleukin 6 (IL-6) in addition to polyclonal hyperimmunoglobulinaemia. High-resolution CT of the chest showed bilateral multiple nodules and patchy ground-glass opacities with interstitial thickening. Biopsy of the cervical lymph node and skin biopsy showed numerous perivascular plasma cells, which were characteristic of the plasma cell type of Castleman's disease. Surgical lung biopsy showed hyalinising granuloma, which are hyaline nodular lesions surrounded by lymphoid cells. He was diagnosed with multicentric Castleman's disease complicated by pulmonary hyalinising granulomas; his symptoms improved by treatment with tocilizumab, which is a humanised antihuman IL-6 receptor monoclonal antibody and corticosteroid. This is the first report of a comorbid case successfully treated with tocilizumab and corticosteroid.

BACKGROUND

Castleman's disease was first described in 1956 as a disease of localised angiofollicular lymph node hyperplasia.¹ From this, a multicentric form of Castleman's disease was identified by Gaba *et al*.² Multicentric Castleman's disease has systemic manifestations that include frequent fevers, night sweats, fatigue, weight loss and peripheral lymphadenopathy. In laboratory examinations, patients with multicentric Castleman's disease have shown evidence of anaemia, hyperimmunoglobulinaemia, and elevated levels of C reactive protein, erythrocyte sedimentation rate and interleukin 6 (IL-6). Dysregulated overproduction of IL-6 by germinal centre B cells has been implicated in the pathogenesis of multicentric Castleman's disease.³ Tocilizumab, a humanised antihuman IL-6 receptor monoclonal antibody, has been reported to be effective in treating multicentric Castleman's disease.⁴

Pulmonary hyalinising granuloma was first described by Engleman *et al*.⁵ It was identified as a rare pulmonary disease of unknown aetiology, and, histologically, it was characterised by nodular lesions including hyaline lamellar collagen.^{5,6}

The first case of combined pulmonary hyalinising granuloma and multicentric Castleman's disease was reported by our hospital in 1994.⁷ This is another case of combined pulmonary hyalinising

granuloma and multicentric Castleman's disease, which was effectively treated with tocilizumab and corticosteroid. We believe that our results are suggestive of a pathophysiological link between the two conditions.

CASE PRESENTATION

A 49-year-old man presented with symptoms of low-grade fever, general fatigue and weight loss. On physical examination, multiple superficial lymphadenopathies and brown macules were observed on the patient's trunk (figure 1). However, any clinical symptoms suggestive of collagen vascular disease, including polyarthralgia or sicca syndrome, were not observed.

INVESTIGATIONS

Laboratory results revealed a normal white cell count, anaemia (haemoglobin 8.3 g/dL), hyperproteinaemia (total protein 8.7 g/dL), polyclonal hyperimmunoglobulinaemia (IgG 4696 mg/dL), and elevated levels of platelets ($41 \times 10^4/\mu\text{L}$), C reactive protein (13.4 mg/dL) and IL-6 (52.5 pg/mL). Chest X-rays showed multiple nodules that were bilaterally diffuse. A high-resolution CT of the chest revealed multiple, bilaterally irregular nodules and ground-glass opacities with interstitial thickening (figure 2A,B). A biopsy of the right cervical lymph node showed medium-sized lymphoid follicles with germinal centres surrounded by plasma cells external to the follicles (figure 3A,B); moreover, a skin biopsy of a macule showed numerous perivascular plasma cells. These findings in the lymph node and skin were characteristics of the plasma cell type of multicentric Castleman's disease. Lung specimens obtained by

Figure 1 Truncal skin lesions on admission showing multiple brown macules.

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Figure 2 (A) A chest radiograph obtained on admission showing multiple nodular opacities in both lungs. (B) High-resolution CT of the chest showing multiple bilaterally irregular nodules (nodules are a few millimetres to a few centimetres in diameter) and ground-glass opacities with interlobular septal thickening.

video-assisted thoracoscopic surgery of the right upper lobe showed hyalinous nodular lesions surrounded by lymphoid cells (figure 4A,B). Based on our results, the patient was diagnosed with multicentric Castleman's disease complicated with pulmonary hyalinising granuloma.

DIFFERENTIAL DIAGNOSIS

Collagen vascular diseases and other diseases were excluded by clinical symptoms and laboratory findings. In this case, our diagnosis of multicentric Castleman's disease was based on the findings of the cervical lymph node biopsy. However, for the differential diagnosis of pulmonary nodules, we performed video-assisted thoracoscopic lung biopsy to exclude Kaposi's sarcoma, malignant lymphoma, amyloidosis and other diseases. Finally, we diagnosed the case as a combination of multicentric Castleman's disease and comorbid pulmonary hyalinising granuloma.

TREATMENT

After diagnosis, prednisolone (25 mg daily) was administered for 3 months. The patient then became afebrile from the treatment, but this was insufficient to ameliorate general malaise. Thus, tocilizumab, a humanised antihuman IL-6 receptor

Figure 3 (A) Excisional biopsy of the right cervical lymph node. The lymph node showed a layer of plasma cells with a width of 200–300 μ surrounding the lymphoid follicles, some of which had germinal centres (H&E stain, magnification $\times 4$). (B) Higher magnification of the square frame in figure 3A. Plasma cells with a width of 300 μ surrounding a lymphoid follicle with clusters of Russell bodies are marked (arrows). Histopathological characteristics of the lymph nodes suggest a plasma cell variant of Castleman's disease (H&E stain, magnification $\times 40$).

monoclonal antibody, was administered (8 mg/kg, biweekly intravenously) in addition to prednisolone. Following treatment with tocilizumab, the patient experienced improvements in general malaise. After 4 months, abnormal laboratory findings of the patient were successfully resolved (table 1).

In addition, some pulmonary nodules were found to have reduced in size and ground-glass opacities were decreased during the course of treatment (figure 5). The size of the right cervical lymph node and skin eruption were not changed. Overall, the hyalinising granuloma appeared to stabilise.

OUTCOME AND FOLLOW-UP

The patient has since been treated for 50 months without significant adverse events. His treatment is still continuing.

DISCUSSION

Castleman's disease has been characterised by solitary hyperplastic mediastinal lymph nodes with small germinal centres resembling thymic Hassall's corpuscles.¹ It has been classified into two histopathological types: hyaline vascular and plasma cell types.⁸ The hyaline vascular type shows germinal centres and onion skin layering of lymphocytes in the mantle zone of the germinal centres, whereas, the plasma cell type shows prominent

Figure 4 (A) Surgical biopsy of the lung from the right middle lobe. The lung tissue showed a nodular lesion that was observed on high-resolution CT. The lesion measured 11×7 mm and consisted of rope-like hyaline material and clusters of lymphoid cells (H&E stain, magnification ×4). (B) Higher magnification of the square frame in figure 4A. Some of the rope-like hyaline material was formed around small blood vessels. In and around the nodular lesion measuring 11×7 mm, plasma cells with clusters of Russell bodies were observed (arrow). The lung lesion was diagnosed as pulmonary hyalinising granuloma using histopathology (H&E stain, magnification ×40).

interfollicular stroma, that is rich in plasma cells and small vessels. Multicentric Castleman's disease is primarily characterised by the plasma cell type. Histological findings of cervical lymph nodes

Table 1 Laboratory findings and treatment

	On admission	At 3 months with corticosteroid	At 4 months with tocilizumab and corticosteroid
Hb (g/dL)	8.3	9.3	13.4
Plt ($\times 10^4/\mu\text{L}$)	41	44	26.5
TP (g/dL)	8.7	7.5	6.4
CRP (mg/dL)	13.4	10.6	0.4
IgG (mg/dL)	4696	3895	1826
SIL-2R (U/mL)	2520	3600	596

CRP, C reactive protein; Hb, haemoglobin; Plt, platelets; SIL-2R, serum soluble interleukin-2 receptor.

and skin in this patient were consistent with the plasma cell type of multicentric Castleman's disease.

Lung biopsy specimens showed hyaline nodular lesions surrounded by lymphoid cells, consistent with pulmonary hyalinising granuloma. Higher magnification of a nodular lesion showed rope-like collagen around the small blood vessels, which had some similarities to the manifestations of the hyaline vascular type of multicentric Castleman's disease.

In 1994, we reported the first case of combined pulmonary hyalinising granuloma and multicentric Castleman's disease.⁷ The frequency of hyalinising granuloma complicated by multicentric Castleman's disease is low, perhaps because these conditions may not be precisely clarified as surgical lung biopsy is not always performed in the diagnosis of pulmonary lesions of this disease. Thus, hyalinising granuloma might not be as rare as expected. Hence, we suspect that hyalinising granuloma could be one of the pulmonary pathological patterns in multicentric Castleman's disease.

This is the first successful tocilizumab-treated case of combined multicentric Castleman's disease and pulmonary hyalinising granuloma. Inhibition of IL-6, which is a key molecule in the clinical development of multicentric Castleman's disease, has resolved this disease, and, at the same time, has led to the stabilisation of the hyalinising granuloma in this case. Thus, we suspect that hyalinising granuloma may be aetiologically associated with multicentric Castleman's disease, and that IL-6 may function as a pathogenic cytokine of hyalinising granuloma.

The aetiological association between pulmonary hyalinising granuloma and multicentric Castleman's disease, as well as the

Figure 5 CT showing a solid nodule in the lingula on admission (A) at 3 months with corticosteroid, (B) at 7 months with tocilizumab and corticosteroid, and (C) the nodule had reduced in size and ground-glass opacities were decreased during the course of treatment.

effectiveness of tocilizumab, should thus be confirmed in future studies.

Learning points

- ▶ The possibility of pulmonary hyalinising granuloma should be considered when multiple nodular lesions are observed in lungs with multicentric Castleman's disease.
- ▶ Surgical lung biopsy is required for the definite diagnosis of pulmonary hyalinising granuloma.
- ▶ Tocilizumab and corticosteroid might be effective in comorbid cases of the two conditions.

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Contributors NT and TA were involved in the treatment and management of the patient. MK was involved in the pathological diagnosis of the patient. YI was involved in the management and laboratory tests of the patient.

Competing interests None.

Patient consent Obtained.

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