CASE REPORT

Antemortem diagnosis with multiple random skin biopsies and transbronchial lung biopsy in a patient with intravascular large B-cell lymphoma, the so-called Asian variant lymphoma

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SUMMARY

A 59-year-old, previously healthy man presented to our hospital, with a 3-month history of high fever, nocturnal sweating and exertional dyspnoea. Aggressive diagnostic procedures such as multiple random skin biopsies and transbronchial lung biopsy (TBLB) led to an antemortem diagnosis of intravascular large B-cell lymphoma (IVLBCL), which showed abundant CD20 atypical lymphocytes aggregated in lumina of small vessels. The 29 cases diagnosed with IVLBCL during their lifetime by TBLB were reviewed. Their clinical features included respiratory symptoms (hypoxaemia, dyspnoea and dry cough) and persistent fever. IVLBCL patients show various radiological patterns (ground glass opacities, multiple centrilobular nodules, interlobular septal thickening, interstitial shadows and thickening of bronchovascular bundles), suggesting lymphatic or haematological spread. Antemortem diagnosis of IVLBCL is difficult, but a multidisciplinary approach, with aggressive multiple random skin biopsies and/or TBLB, should be considered in patients with respiratory symptoms that are refractory to antibiotics or prednisolone treatment.

BACKGROUND

On the basis of the previous reports, antemortem diagnosis of intravascular large B-cell lymphoma (IVLBCL) is difficult. Therefore, a multidisciplinary approach is required for prompt diagnosis. The case of a 59-year-old, previously healthy man presented to our department with fever and respiratory symptoms is described. He was successfully diagnosed with IVLBCL by transbronchial lung biopsy (TBLB) and multiple random skin biopsies, and then treated appropriately. To further explore the clinical clues to the diagnosis, a literature review of cases with IVLBCL who had antemortem diagnosis by TBLB was performed, and their clinical, radiological and laboratory aspects were characterised.

CASE PRESENTATION

A 59-year-old, previously healthy man presented to our hospital, with a 3-month history of high fever, nocturnal sweating and exertional dyspnoea. At a local hospital, based on the radiological findings, he was tentatively diagnosed with summer-type hypersensitivity pneumonitis or idiopathic interstitial pneumonia and treated with various antibiotics with intravenous steroid pulse therapy (1000 mg/day), followed by oral prednisolone (1 mg/kg/day). He was then treated with oral prednisolone with a tapering

dose of 15 mg/day for 2 months prior to coming to our hospital. He was an ex-smoker with a smoking history of 200 pack-years. He had worked as a taxi driver for 40 years and denied any dust exposure or illicit drugs. At his initial presentation (day 1), he appeared well, and vital signs showed blood pressure of 112/60 mm Hg, temperature 38.2°C, heart rate 94 beats/min, respiratory rate 16 breaths/min and oxygen saturation 88% on ambient air. Physical examination showed net-like erythema on the body trunk and proximal extremities, and no inspiratory fine crackles or superficial lymphadenopathy was noted. Chest X-ray (figure 1A) showed faint infiltration that diffusely expanded throughout both lungs, especially in the middle-to-lower areas. Gadolinium-enhanced thoracoabdominal CT showed moderate splenomegaly, and diffuse ground glass opacities (GGOs) (figure 1B) were seen throughout the whole lung, predominantly located in bilateral middle-to-lower lobes accompanied by interlobular septal thickening. Serum laboratory examinations showed mild elevations of leucocyte count (11 000/ μ L), glutamate pyruvate transaminase (83 IU/L) and surfactant protein D (132 ng/mL), and marked elevation of lactate dehydrogenase (LDH; 605 IU/L), C reactive protein (19.5 mg/dL), procalcitonin (9.6 ng/mL) and soluble interleukin-2 receptor (sIL2R; 2320 U/mL). Serum Krebs von den Lungen-6 (429 U/mL) was normal, and anti-HIV and antihuman T-cell leukaemia virus type 1 antibodies were negative.

Figure 1 (A) Chest X-ray taken on admission showing faint infiltration diffusely throughout both lungs, especially in middle-to-lower areas. (B) Chest CT scan taken on admission showing diffuse ground glass opacity (GGO) in the left upper and lingular lobes, accompanied by interlobular septal thickening.

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Figure 2 On H&E stain ($\times 200$), transbronchial lung biopsy specimens obtained from right B2 and B8 show accumulation of abundant atypical lymphocytes in the capillary vessels (A), which are more clearly recognised in the high-power field (B). The atypical lymphocytes are positive for immunohistochemical staining with CD20 (C), and Elastica van Gieson stain confirms that these atypical cells are mainly located in the intraluminal space and are partially extravasated into the perivascular area (D).

On the basis of these clinical findings, such as the long prodromal phase lasting up to 3 months with high fever, nocturnal sweating, exertional dyspnoea and skin lesions, together with various radiological patterns showing diffuse GGO and interlobular septal thickening, he was suspected of having intravascular lymphoma, the so-called Asian variant lymphoma, or diffuse large B-cell lymphoma.

INVESTIGATIONS

A TBLB was immediately performed on the day of admission. On H&E staining, the biopsied specimens (figure 2A, B) showed accumulation of abundant atypical lymphocytes in the capillary vessels, which were immunohistochemically stained by

CD20 (figure 2C) and CD79a (figure not shown), suggesting B-cell lymphoma. Elastica van Gieson stain confirmed that these atypical cells were mainly located in the intraluminal space and partially extravasated to the perivascular area (figure 2D). Bone marrow biopsy specimens showed hypocellular bone marrow, but no atypical lymphocytes were noted. The net-like erythema on the body trunk and proximal extremities regressed on day 2 and disappeared on day 7. However, multiple random skin biopsy specimens taken at day 7 obtained from the right upper arm on the flexor aspect showed that atypical lymphocytes have accumulated in the capillary vessels of the subcutaneous dermal fat (figure 3A, $\times 100$). On high-power field examination, the numerous CD20 atypical lymphocytes (figure 3B, C) packed the lumina of small vessels.

Figure 3 Multiple random skin biopsy specimens obtained from the right upper arm on the flexor aspect show that atypical lymphocytes have accumulated in the capillary vessels of the subcutaneous dermal fat (A, $\times 100$). On high-power field examination, the numerous CD20 atypical lymphocytes (B and C) pack the lumina of small vessels.

Table 1 Twenty-nine case reports of IVLBCL diagnosed by TBLB

Age	Sex	LDH (IU/L)	sIL-2R (U/mL)	Skin lesion	Random skin biopsy	Bone marrow biopsy	Chest CT findings		Reference
							Patterns	Distribution	
56	M	1298	NA	—	—	NS	Nodules	Lower lung fields	¹
58	M	NA	NA	—	—	NS	NS	NA	¹
60	M	1200	NA	—	—	NS	Centrilobular nodules	NA	¹
53	F	5085	NA	—	—	—	GGO	Diffuse	¹
63	M	1825	NA	—	—	NS	Mosaic attenuation	Lung bases	¹
71	M	1976	3750	—	—	NS	GGO	Without lung bases	¹
65	M	2387	3380	—	—	NS	Reticulonodular shadows	Upper lungs	¹
65	M	2327	1820	—	—	—	Consolidation, thickening of bronchovascular bundles	Right lower lobe	¹
49	F	5938	NA	—	—	NS	Consolidation	Left upper lung	¹
68	F	1040	1760	—	—	—	Migratory consolidation	NA	¹
72	F	1494	1970	—	—	—	Centrilobular nodules	NA	¹
45	M	787	2090	—	—	—	Low attenuation	Upper lobes	¹
65	M	1625	2105	—	Yes	Yes	Interstitial shadows	NA	¹
73	M	1248	5290	Yes	Yes	Yes	Interstitial shadows	NA	¹
50	F	3386	6499	—	—	NS	NS	NA	¹
54	F	2040	1347	—	—	NS	GGO	Upper, middle lung fields	¹
46	M	1347	767	—	—	NS	Reticulonodular shadows	Diffuse	¹
54	F	2145	1870	—	—	Yes	GGO, interlobular septal thickening	Diffuse	¹
61	M	1649	1827	—	—	NS	Reticulonodular shadows	Lower lung fields	²
70	M	1205	1860	—	—	NS	GGO	Diffuse	³
70	M	2143	2470	—	—	NS	Nodules	Diffuse	⁴
71	F	595	728	—	—	Yes	GGO	Upper lobes	⁴
55	M	1480	4140	—	—	NS	GGO	Diffuse	⁵
39	M	2214	1950	—	—	—	NS	NA	¹
58	F	570	3699	—	—	NS	NS	NA	¹
61	M	698	4130	—	—	—	NS	NA	⁶
84	M	641	2238	—	—	NS	NS	NA	⁷
67	F	490	2500	—	—	NS	GGO	Apical portions	⁸
59	M	605	2320	Yes	Yes	NS	GGO	Diffuse	Present case

GGO, ground glass opacity; IVLBCL, intravascular large B-cell lymphoma; LDH, lactate dehydrogenase; NA, not available; NS, no specific findings; sIL-2R, soluble interleukin-2 receptor; TBLB, transbronchial lung biopsy.

lumina of small vessels, which were also stained with CD5 (figure not shown). Thus, he was diagnosed with IVLBCL, the so-called Asian variant lymphoma.

OUTCOME AND FOLLOW-UP

After the diagnosis, he was moved to the haematology ward and treated with intravenous rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), doxorubicin hydrochloride (hydroxydaunorubicin; 50 mg/m²), vincristine (oncovin; 1.4 mg/m²) and oral prednisone (20 mg/day), the so-called R-CHOP therapy. He was then discharged uneventfully and was scheduled to receive repeated chemotherapy with the same regimen.

DISCUSSION

IVLBCL was first described by Pfleger and Tappeiner in 1959, and over 300 cases have been reported so far. IVLBCL is a rare subtype of diffuse large B-cell lymphoma that is characterised by tumour cells that pack the lumina of small vessels without infiltrating into parenchymal tissue. This was mainly considered to be due to two factors: (1) tumour cells lack CD29 (β1 integrin) and CD54 (intercellular adhesion molecule (ICAM)-1), which are essential for lymphocyte homing and transvascular migration; (2) aberrant expression of CD11a and CD49d (very late antigen (VLA)-4) on tumour cells enables them to stay in the

luminal space via attachment to endothelial cells. Thus, parenchymal and bone marrow infiltration by tumour cells is not recognised until the progressive stage, which is why antemortem diagnosis of IVLBCL is difficult. Furthermore, IVLBCL has extremely heterogeneous clinical presentations, such as fever of unknown origin, central nervous system involvement, cutaneous involvement and haemophagocytosis. Therefore, antemortem diagnosis is a challenging, critical issue for physicians. In this regard, 29 reports, including the present case, in the medical literature of successful antemortem diagnosis by TBLB were reviewed (table 1).^{1–8} In these patients, the male-to-female ratio was 19 : 10, with an age range from 45 to 84 years (mean age ±SD, 60.8±9.9 years).

Their main clinical findings were fever (n=25, 86%), hypoxaemia (n=20, 69%), dyspnoea (n=18, 62%) and dry cough (n=8, 28%). The present case had all these clinical findings except for dry cough. However, some patients showed hepatosplenomegaly (n=11, 38%) and two patients showed nervous system symptoms (headache or dementia). The serum laboratory examinations were non-specific, but marked elevations of LDH (from 490 to 5938 U/L; median value, 1487 U/L) and sIL2R (from 728 to 6499; median value, 2105 U/mL) were seen, as in the present case. Of note, none of the patients had superficial or mediastinal lymphadenopathy. Currently, random skin biopsy has been reported as a useful diagnostic tool

Learning points

- ▶ Respiratory symptoms such as hypoxaemia, dyspnoea and dry cough, together with persistent fever, which are refractory to treatment with antibiotics or prednisolone, might be characteristic clinical features of intravascular large B-cell lymphoma (IVLBCL), especially with pulmonary involvement.
- ▶ Although no superficial or mediastinal lymphadenopathy was noted, marked elevations of serum lactate dehydrogenase and/or soluble interleukin-2 receptor are clinical clues to the diagnosis of IVLBCL.
- ▶ On thoracic CT, IVLBCL patients have various radiological patterns, including ground glass opacities, multiple centrilobular nodules, interlobular septal thickening, interstitial shadows and thickening of bronchovascular bundles, suggesting lymphatic or haematological spread.
- ▶ Antemortem diagnosis of IVLBCL is difficult, but aggressive multiple random skin biopsies should be considered even if no skin lesions are noted.

with high sensitivity (83.3%) for IVLBCL,⁹ and all three patients in the review who underwent skin biopsy with (n=2, one of which is the present case) or without (n=1) skin lesions demonstrated the presence of tumour involvement. These findings suggest that aggressive random skin biopsy together with TBLB would lead to a prompt antemortem diagnosis. In the literature review, bone marrow biopsies were obtained from 22 patients, but only 3 patients (13.6%) showed positive results for IVLBCL. In the review of the thoracic CT findings, all patients had diverse radiological patterns, including GGO, multiple centrilobular nodules, interlobular septal thickening, interstitial shadows and thickening of bronchovascular bundles, suggesting lymphatic or haematological spread. Regarding GGO, it

seemed to be visible throughout the whole lungs (n=12, 41.4%). Thus, radiological diagnosis of IVLBCL was difficult, but general physicians should be aware of the possibility of IVLBCL whenever they encounter febrile patients with respiratory symptoms such as hypoxaemia, dyspnoea and dry cough that are refractory to treatment with antibiotics or prednisolone.

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Competing interests None.

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