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Pulmonary intravascular lymphoma mimicking hypersensitivity pneumonitis

Santos et al. have recently characterized hypersensitivity pneumonitis (HP).[1] HP is diagnosed based on the patient's exposure history, physical examination (dyspnea, cough, and fever) findings, chest high-resolution computed tomography (HRCT) findings, and bronchoalveolar lavage (BAL). Santos et al. reported that most patients with HP exhibit respiratory symptoms (dyspnea and cough); and ground-glass opacification (GGO) occurred in thoracic CT of 76.7% acute and 91.7% subacute HP cases. HRCT features, including centrilobular diffuse nodules, ground-glass opacification (GGO), and mosaic attenuation, are especially useful for diagnosis.[1,2] Although these typical CT patterns are often useful in clinical practice, sometimes, they may also be present in other diseases. Through our recent clinical experience, we wish to highlight a pulmonary intravascular lymphoma with diffuse centrilobular GGO mimicking HP.

A 61-year-old man with no medical history who was a non-smoker and took no medications was admitted to our hospital with fever (38.5 °C), dyspnea, and cough. He had hypoxemia (SpO_2 88% at room air) but no crackles. He did not present with extrapulmonary symptoms. Blood tests revealed high C-reactive protein (4.2 mg/dL), lactate dehydrogenase (LDH) (923 U/L), and soluble interleukin-2 receptor (sIL-2R) (609 U/mL) levels. Serological tests for anti-neutrophil cytoplasmic antibody and other known autoantibodies against specific antigens were all negative. Chest HRCT revealed diffuse centrilobular GGO and nodules in the bilateral lungs (Fig. 1A). We initially suspected HP based on the respiratory symptoms, CT findings, and history of a dusty air conditioner at the patient's workplace. Although he was observed carefully without receiving steroid therapy to avoid antigens, his symptoms worsened; his LDH and sIL-2R levels increased. We could not perform BAL because of hypoxemia. Histological examination of a transbronchial lung biopsy (TBLB) specimen showed abnormal lymphocytes in the intravascular space of the capillaries (Fig. 1B). Immunohistochemical staining revealed that the tumor cells were positive for vascular antigens, including CD20, CD79α, and Ki-67 (Fig. 1C–E). Based on these findings, we diagnosed pulmonary intravascular large B-cell lymphoma (IVLBCL). Thereafter, he received chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisolone. His symptoms improved, and the diffuse opacities mostly disappeared.

IVLBCL is a rare extranodal subtype of non-Hodgkins lymphoma characterized by the selective growth of malignant lymphocytes within the blood vessels, especially in the capillaries, small arteries, and veins.[3] The clinical manifestation of pulmonary IVLBCL is nonspecific, and symptoms include fever, cough, and dyspnea.[4] The appearance on chest HRCT is varied and can include centrilobular nodules, GGO, and interlobular septal thickening.[5] Centrilobular nodules reflect lesions in the bronchioles located at the center of the pulmonary lobules, bronchial arterioles, broad interstitium, and lung parenchyma. In the present case, abnormal lymphocytes had infiltrated the capillary vessels and surrounding space, suggesting that small blood vessels in centrilobular structures can be significantly damaged by intravascular lymphoma. Consequently, we

Table 1 Previous case reports of pulmonary intravascular large B cell lymphoma diagnosed by transbronchial lung biopsy.

No.	Age	Sex	Symptoms	LDH (IU/L)	sIL2R (U/L)	CT imaging	Treatment	Outcome
1	82	Male	Forgetfulness	3040	1263	GGO	R-CHOP	Improvement
2	58	Female	Fever, weight loss	Unknown	6774	Normal findings	Unknown	Unknown
3	60	Female	Dyspnea, fever	1434	Unknown	GGO, nodules	Unknown	Death
4	69	Female	Dyspnea, fever, cough	1095	Unknown	GGO, interlobular septal thickening	CHOP	Unknown
5	69	Female	Fatigue, fever, dyspnea	1475	2771	Normal findings	Unknown	Unknown
6	62	Male	Dyspnea	1482	1570	Nodules	R-CHOP	Complete remission
7	57	Male	Fever, dyspnea	Unknown	Unknown	Haziness	Unknown	Unknown
8	85	Male	Dyspnea	829	2000	GGO	R-CHOP	Improvement
9	59	Male	Fever, dyspnea	605	2320	GGO, interlobular septal thickening	R-CHOP	Improvement
10	35	Female	Cough, dyspnea, fever	1554	Unknown	Consolidation, GGO	R-CHOP	Death
11	46	Male	Cough, fever	765	19100	Nodules, granular shadows	R-CHOP	Complete remission
12	71	Female	Fever	Unknown	Unknown	Normal findings	R-CHOP	Partial response
13	84	Male	Dyspnea	1120	2238	Normal findings	R-CHOP	Complete remission
14	61	Male	Night sweats, dyspnea	698	4130	Normal findings	R-CHOP	Complete remission
15	58	Female	Cough, fever	570	3699	Normal findings	R-CHOP	Improvement
16	39	Male	Dyspnea, fever	2214	1950	Normal findings	R-CHOP	Improvement
17	50	Female	Fever, anorexia, oedema, muscular pain	3386	6499	Normal findings	R-CHOP	Complete remission
18	65	Male	Fever, dyspnea	1625	2105	Interstitial shadows	CHOP	Complete remission
19	73	Male	Fever, dyspnea, skin lesions	1248	5290	Interstitial shadows	CHOP	Complete remission
20	49	Female	Fever, cough	5938	Unknown	Interstitial shadows	Cisplatin, cytarabine, dexamethasone	Improvement
21	65	Male	Dyspnea, dementia	2327	1820	Consolidation, bronchovascular bundles thickening	CHOP	Improvement
22	63	Male	Dyspnea, cough, fever, weight loss	1825	Unknown	Mosaic attenuations	CHOP	Complete remission

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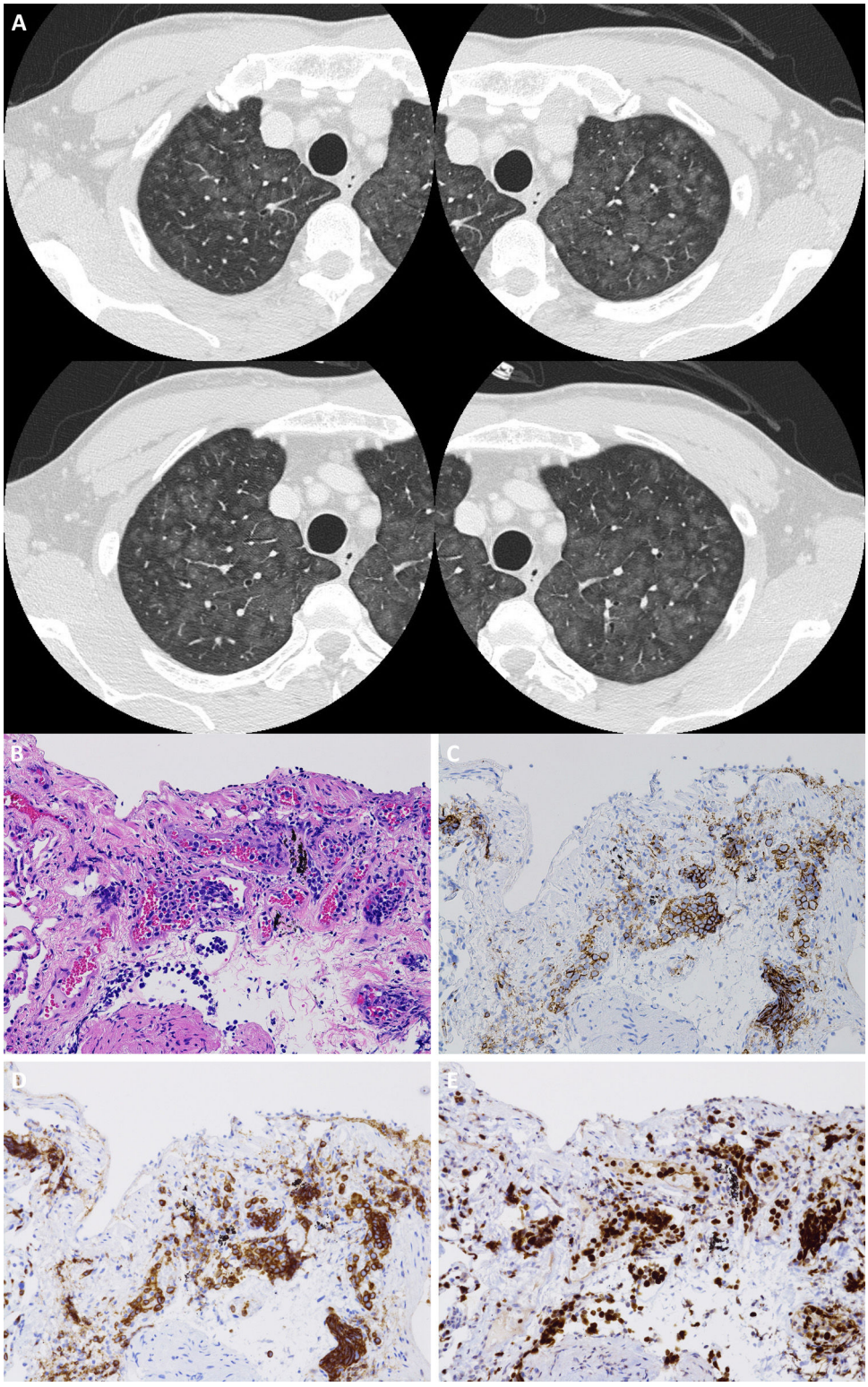

Figure 1 (A) Chest high-resolution computed tomography revealing diffuse ground glass opacities and nodules with centrilobular augmentation in the bilateral lungs. (B) Microphotographs of the transbronchial lung biopsy specimen. Atypical lymphocytes are seen in the intravascular space of capillary blood vessels. Immunochemical staining revealing that these cells were positive for CD20 (C), CD79α (D), and Ki-67 (E).

considered that HRCT revealed HP-like pale GGO and nodules with a centrilobular distribution pattern. It is probable that the resulting occlusive proliferation of tumor cells in the vascular lumens led to multiple minor infarctions, which manifested as coughing, dyspnea, and fever.

IVLBCL is often not identified during the lifetime, is only diagnosed at autopsy. To the best of our knowledge, only 22 cases, diagnosed by TBLB, have been reported during the past 20 years (Table 1). Respiratory symptoms including dyspnea and cough were present in 18 of those 22 cases, and both LDH and sIL2-R were elevated. Thoracic CT revealed GGO and nodules in some cases but was normal in others, and the response to treatment was mostly good. Based on these findings, TBLB may assist with diagnosis in patients complaining chiefly of respiratory symptoms, and early diagnosis may contribute to improved prognosis. TBLB may also be valuable in the differential diagnosis of other diseases, including HP (particularly acute/subacute HP).

Although the diagnosis of pulmonary IVLBCL is difficult due to its nonspecific clinical manifestation, in cases of diffuse centrilobular GGO and nodules on chest HRCT, it is necessary to consider not only HP but also pulmonary IVLBCL. Moreover, increased serum LDH and sIL-2R levels should suggest a diagnosis of IVLBCL, and TBLB be performed to make a definitive diagnosis.

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Poly-resistant tuberculosis outbreak in Northern Portugal: a nine year tale

In 2017, the notification rate of tuberculosis in the Northern Region of Portugal was 21.1 cases per 100 000 inhabitants.[1] According to the National Tuberculosis Programme Surveillance System (SVIG-TB), poly-resistance to isoniazid and streptomycin (PR-HS) represented 2.6–5% of the cases notified in the Northern Region between 2009 and 2017 Although they represent a relatively low proportion of cases in Portugal, poly-resistances such as PR-HS are precursors to multidrug resistance and, consequently, should be closely monitored.[2]

Seventeen cases of pulmonary tuberculosis (TB) with PR-HS were recorded during 2009–2015 in Santa Maria da Feira (SMF), a municipality with 139 312 inhabitants (National Statistics Institute 2011) that belongs to Entre-Douro-e-Vouga-I community health centre cluster (EDVI). This represented a total of 9.3% of the TB notifications in EDVI in this period and was consistently higher than expected in the region (4.1%).

The existence of a cluster of 17 cases with an identical profile of antibacterial resistance led to the generation of the hypothesis of an ongoing TB outbreak. One epidemiological link had been established between two cases, but the remaining cases were apparently not associated. Research was carried out in order to confirm the existence of the outbreak.

Epidemiological surveys performed at the time of notification of PR-HS diagnosed cases from 2009 to 2015 were reviewed by the local Public Health Unit. Cases (or their closest relative alive) were re-interviewed, including clarification of social and occupational history in the two years prior to diagnosis. Specimens of culture-positive cases were sent to the National Mycobacteria Reference Laboratory (INSA) for strain genotyping, using Mycobacterial Interspersed Repetitive Units-Variable Number of Tandem Repeats method (MIRU-VNTR).

All 17 cases included were new cases. Eleven were male (64.7%), with a median age of 50 years (IQR: 22) at the time of diagnosis. All cases had pulmonary involvement, 82.4% were cavitated and 47.1% had positive sputum smear microscopy.

At the time of diagnosis, all cases were resident in SMF. Considering residence and occupation, the review of epidemiological information and the collection of new data made it possible to identify three contiguous parishes (Fig. 1) corresponding to place of residence or work in nine cases (53%).