

## CASE REPORT

# NK/T cell lymphoma of the lung: a case report and review of literature

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Primary lymphoma of the lung is rare and is usually of B cell type. Tissue samplings taken by transbronchial biopsy and computed tomographic (CT) guided needle biopsy of the right perihilar area of an elderly woman who presented with refractory pneumonia showed T cell lymphocytosis with no evidence of active infection. The patient's respiratory status rapidly deteriorated and she eventually died. Post mortem examination revealed primary pulmonary T cell lymphoma with natural killer (NK) cell features. We present what may be the first case of primary NK/T cell pulmonary lymphoma and review the literature on the subject.

Primary pulmonary lymphoma is rare.<sup>1</sup> Most cases are of B cell origin and commonly arise from bronchial mucosa associated lymphoid tissue (MALT).<sup>1</sup> Non-B cell lymphomas—that is, T cell and natural killer (NK) cell lymphomas—involving the lung parenchyma are uncommonly reported. NK/T lymphoma is aggressive and delay in establishing the diagnosis can result in a fatal outcome.

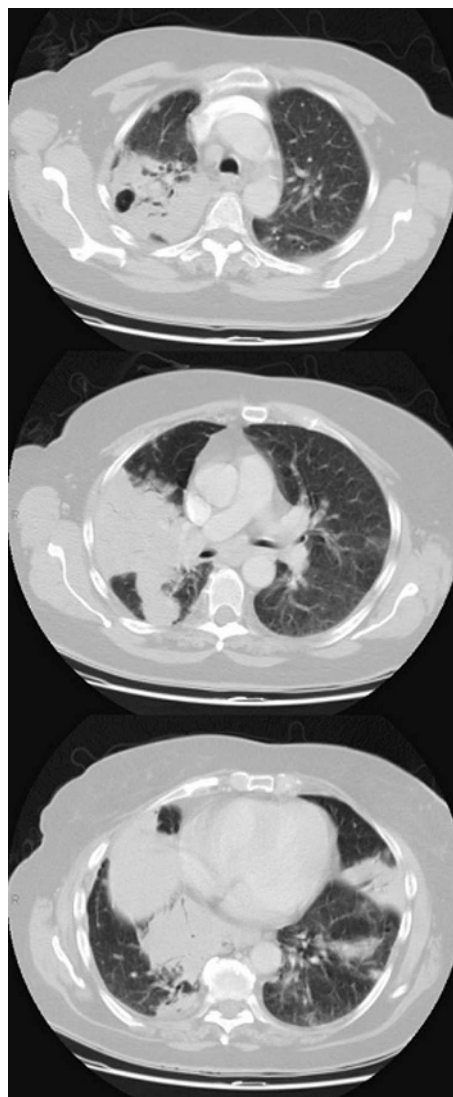
### CASE REPORT

A 72 year old female non-smoker presented with shortness of breath (SOB), productive cough, and intermittent fever for 3 months. She was treated with azithromycin for community acquired pneumonia without improvement. The chest radiograph showed multiple areas of consolidation in the right lung. Initial laboratory findings revealed normal complete blood count and an unremarkable chemistry panel. A computed tomographic (CT) scan of the chest showed bilateral areas of consolidation with cavitation in the right upper lobe and diffusely distributed small nodules. No mediastinal or hilar adenopathy was noted (fig 1). Antibiotic coverage was modified to intravenous doxycycline and cefotaxime. A bronchoscopy with transbronchial biopsy (TBB) was performed. The bronchoalveolar lavage (BAL) fluid revealed 240 white blood cells (WBC)/ml with 80% lymphocytes, and the TBB showed lymphocytic inflammation. Cultures from the BAL fluid subsequently grew group B *Streptococcus* and parainfluenza virus, which were believed to be responsible for the lymphocytic inflammation. She improved and was discharged home only to return to the hospital 2 weeks later with worsening SOB.

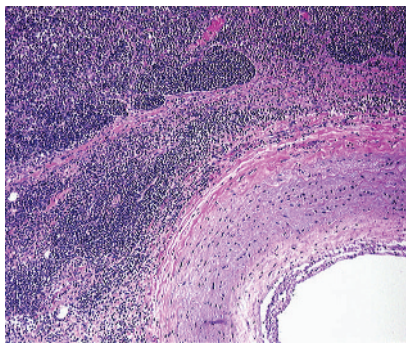
A repeat CT scan of the chest showed increasing consolidation in both lungs without adenopathy and a new right sided pleural effusion. Thoracentesis was performed which also revealed a lymphocytic exudate. Cultures and cytological examination of the pleural fluid were negative. The patient underwent a repeat bronchoscopy with TBB which again indicated lymphocytic infiltration. Gram stain and special stains for atypical organisms including mycobacteria, fungi, and *Pneumocystis carinii* were negative. The BAL fluid cultures were negative. Flow cytometry of the BAL fluid

indicated that more than 80% of the lymphocytes were T cells (CD3+) with a CD4 to CD8 ratio of 0.3.

At this point a clinical suspicion for a T cell lymphoproliferative disorder was raised. A positron emission tomographic (PET) scan was obtained in an attempt to identify the extent of the disease and an alternative site for tissue sampling. The PET scan revealed an isolated intense hypermetabolic uptake in the right middle and lower lung regions without other identifiable adenopathy. An open lung



**Figure 1** Computed tomographic (CT) scans of the chest showing dense consolidated areas in all lobes of the right lung and cavitation of the right upper lobe.



**Figure 2** Lung pathology showing angiocentric infiltration of the lung parenchyma by malignant cells. Stain: H&E; magnification  $\times 400$ .

biopsy was recommended to the patient which she declined. A CT guided transthoracic needle biopsy of the right perihilar area was therefore undertaken which revealed CD3+, CD20–, and CD56+ cells indicating that the cells were of T and NK cell lineages. The new finding of CD56+ lymphocytes increased the likelihood of an atypical lymphoproliferative process involving NK cells, but it cannot be considered pathognomonic for a malignant process. T cell receptor (TCR) gene rearrangement was attempted but was unsuccessful due to paucity of viable cells. The patient's clinical condition deteriorated. She refused further evaluation and developed progressive respiratory failure and died.

Post mortem examination showed multiple masses in both lungs, hilar and mediastinal lymphadenopathy. On microscopic examination the lung tissues and enlarged lymph nodes contained uniform, round, small cells with a high nucleus to cytoplasm ratio supportive of a malignant process. The cells were angiocentric and angioinvasive (fig 2). Special staining for leucocyte common antigen (LCA) was positive (fig 3A). The cells stained positive for CD3 and CD56 but negative for CD20 (fig 3B). As CD3 is a T cell marker, CD56 is an NK cell marker, and CD20 is a B cell marker, the immunocytochemistry showed that the malignant lymphoma cells were of T and NK lineages. TCR gene rearrangement could not be done because of the lack of viable cells at post mortem examination. Based on the neoplastic morphology and the destructive nature of the CD3+ CD56+ lymphocytes, the pathological diagnosis was primary T cell lymphoma of the lung with the possibility of NK cell overlap.

## DISCUSSION

Apart from HIV related lymphoproliferative disorders, primary lymphoma of the lung is rare.<sup>1</sup> While extranodal

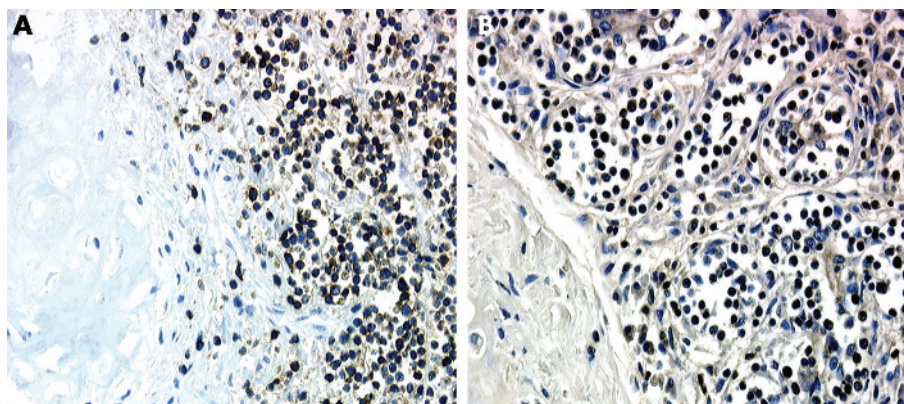
manifestations of non-Hodgkin's lymphoma (NHL) are not uncommon, isolated involvement of the lung is found in only 3–4% of cases.<sup>1</sup> Most cases reported are B cell lymphoma.<sup>2</sup> The true incidence of pulmonary lymphomas other than B cell type is unknown. Tamura and co-workers<sup>2</sup> reported 24 cases of primary pulmonary lymphoma, only one of which was T cell in origin. Since 1990 only 13 cases of non-B cell pulmonary lymphoma have been reported. Most of these reports are not in English. Eleven of the 13 cases are reviewed here.<sup>3–13</sup> The clinical characteristics of these cases are summarised in table 1.

The patients were usually elderly, with a female to male ratio of approximately 2:1. Most of the cases presented with cough and dyspnoea. Only three patients were asymptomatic and were diagnosed after incidental discovery of an abnormal chest radiograph.<sup>6 7 13</sup> The most common radiographic finding was bilateral diffuse nodular lesions.<sup>3 5 7 9 12</sup> Mass-like consolidation,<sup>10 11 13</sup> cryptogenic organising pneumonia (COP)-like lesions,<sup>4 8</sup> hilar adenopathy,<sup>3</sup> and pleural effusion<sup>11</sup> were also reported. These radiographic features are also associated with bronchial MALT lymphoma<sup>1</sup> and cannot be used to differentiate between non-B cell and B cell malignancy of the lung.

TBB was non-diagnostic in nine of the 11 cases. Transbronchial needle aspiration (TBNA) was obtained in one case,<sup>13</sup> which was also non-diagnostic. Limited flow cytometry on BAL fluid (CD4/CD8 subpopulation analysis only) was done in two cases.<sup>7 12</sup> An open lung biopsy (OLB) or lobectomy was eventually required in nine cases.<sup>4–10 12 13</sup> The other two cases were diagnosed by an endobronchial biopsy of a well visualised mass,<sup>11</sup> and by a cervical lymph node excisional biopsy.<sup>3</sup> Immunocytochemistry of the surgical biopsy specimens showed T cell markers in all cases. None of the cases reported simultaneous NK cell markers on the tumour cells. Genotypic assessment—that is, TCR gene rearrangement—was not reported in any of the cases.

Treatment consisted of CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) based chemotherapy in eight patients with varying success. Four patients subsequently died and four were still living by the time the reports were published. Boon *et al*<sup>4</sup> and Hanawa *et al*<sup>8</sup> reported dramatic clinical and radiographic response to systemic corticosteroid alone without chemotherapy. In one case<sup>4</sup> corticosteroid was used as a temporary measure until the patient could tolerate OLB.

Surgical resection was performed on three patients.<sup>6 10 13</sup> In two cases the tumours were focal and the lobectomy led to cure. The pathology and immunocytochemistry of the third patient showed mixed T cell lymphoma and squamous cell carcinoma of the lung. Adjuvant chemotherapy for lym-



**Figure 3** Immunocytochemistry showing that the malignant cells stained positive for (A) leucocyte common antigen (LCA) and (B) CD3. Magnification  $\times 400$ .

**Table 1** Summary of reported cases of primary pulmonary T cell lymphoma since 1990

Reference	Age	Sex	Presentation	Radiographic findings	Diagnostic intervention	Treatment and outcome
Asano <sup>3</sup>	75	F	Dyspnoea	Multiple nodules, hilar adenopathy	Cervical lymph node biopsy	Chemotherapy with complete remission, alive*
Maehara <sup>11</sup>	70	F	Productive cough, fever	L pleural effusion, LLL mass	Endobronchial biopsy	Chemotherapy, alive*
Boon <sup>4</sup>	63	M	Fever	COP-like	OLB	Chemotherapy, died
Fujihara <sup>5</sup>	69	F	Abnormal CXR	LLL nodule	Lobectomy	Lobectomy, alive*
Hanada <sup>7</sup>	42	M	Abnormal CXR	Multiple lung nodules	OLB	Chemotherapy, alive*
Maejima <sup>12</sup>	29	M	Dyspnoea	Multiple lung nodules	OLB	Chemotherapy, CNS relapse and died
Sasaki <sup>13</sup>	65	F	Abnormal CXR	RML, RLL infiltrates	RML and RLL lobectomy	Lobectomy with residual disease, alive*
Hanawa <sup>8</sup>	52	M	Recurrent infiltrates	COP-like	OLB	Systemic corticosteroid, alive*
Karakus <sup>9</sup>	48	F	Cough, dyspnoea	Multiple lung nodules	OLB	Chemotherapy with partial remission, alive*
Kawashima <sup>10</sup>	74	F	Cough, haemoptysis	RLL mass	Lobectomy	Lobectomy and chemotherapy, died
DeTorres <sup>5</sup>	68	F	Fever, weight loss	Multiple lung nodules	OLB	Chemotherapy, died

\*At the time the report was published.

F, female; M, male; LLL, left lower lobe; RML, right middle lobe; RLL, right lower lobe; COP, cryptogenic organising pneumonia; OLB, open lung biopsy; CXR, chest x ray; CNS, central nervous system

phoma was given after surgery. Despite the combined treatments, the patient died.

Compared with pulmonary B cell lymphoma, the outcome of patients affected by non-B cell lymphoma of the lung is much worse. Pulmonary bronchial MALT lymphoma is indolent and confers a median survival time of more than 10 years.<sup>1</sup> Even in high grade B cell lymphoma of the lung, the median survival time is estimated to be 8–10 years.<sup>1</sup> Immunotyping of the tumour is therefore crucial to determine the prognosis.

Non-B cell lymphoma of the lung presents a diagnostic challenge in clinical practice. To differentiate between a reactive process and a T cell malignant disease, monoclonality of the T cells needs to be demonstrated.<sup>14</sup> Because each antigen-specific T cell and its clonal progeny has a unique rearrangement of its TCR gene, rearrangement of the TCR gene is essential to establish monoclonality. The World Health Organization (WHO) and revised European-American classification of lymphoid neoplasms (REAL) defines extranodal T cell or NK cell neoplasms based on their anatomical sites, phenotype, and genotype.<sup>14, 15</sup> Histopathological examination usually reveals cytological dysplasia, homogeneous populations of cells, and marked architectural effacement. Although non-specific, morphological features are useful in directing the subsequent work-up for diagnosis. Immunophenotyping using immunohistochemistry or the much more sensitive flow cytometry is valuable in defining the lineage of origin. Finally, the clonality is demonstrated by TCR gene rearrangement. The combination of histopathology, phenotype (flow cytometry) and genotype (TCR gene rearrangement) in conjunction with the anatomical site of presentation is essential to the diagnosis of extranodal T cell lymphoma as not one parameter is entirely specific.<sup>15</sup> Certain profiles on flow cytometry can suggest a lymphoproliferative process but flow cytometry is not specific enough to use as a single definitive test to diagnose extranodal T cell lymphoma. Adequate viable tissue is a prerequisite to a reliable result, especially for phenotypic and genotypic studies.

In our case the T lymphocytic infiltration of the lung was initially viewed as a reaction to an infectious process. The clues that led to the clinical suspicion of non-B cell lymphoma included persistent T cell lymphocytosis with NK cell features of the lung and absence of a definitive infectious process. A needle aspiration of the right perihilar area provided a scant amount of cells bearing CD3 and CD56 markers which was insufficient for TCR gene rearrangement. Without adequate tissue to establish a definite diagnosis,

treatment could not be initiated and her clinical course rapidly deteriorated due to the virulent nature of non-B cell lymphoma.

A transbronchial needle aspiration (TBNA) or Wang needle aspiration may have a role in obtaining a clinical specimen for TCR gene rearrangement when thoracic lymphadenopathy is present. However, one third of all T cell lymphomas and virtually all NK cell tumours arise at extranodal sites.<sup>14</sup> As shown in table 1, most cases of pulmonary T cell lymphoma presented with isolated lung parenchymal lesions without thoracic lymphadenopathy. Only one of the 11 cases reported hilar adenopathy.<sup>3</sup> In our case, hilar and mediastinal adenopathy was not detected by CT scan or PET scan but was present at post mortem examination. This could be explained by the fact that the lymph nodes were adjacent to the mass-like parenchymal lesion which might have obscured the presence of distinct lymphadenopathy.

CD56 positive T cell lymphoma (or NK/T cell lymphoma) is a very aggressive neoplasm. According to the WHO and REAL classifications, this group of lymphomas is now referred to as "extranodal NK/T cell lymphoma, nasal and nasal-type".<sup>14</sup> They are characterised by extranodal presentation, angiocentric and angiodestructive proliferation.<sup>14</sup> Sinonasal disease is a usual finding, although skin and aerodigestive mucosae are not uncommonly involved. The lung is usually involved as a metastasised organ. Typically, the cells bear CD56 on the surface, with or without CD3.<sup>14</sup> CD20 is usually absent. Prognosis is variable, with long term survival ranging from 20% to 80%. Patients with early stage and non-bulky disease tend to have a better prognosis.<sup>14</sup> In our patient the lymphoma cells stained positive for CD3 and CD56 and showed an angiocentric preponderance. However, the post mortem examination did not reveal upper respiratory tract involvement of the lymphoma, which is a clinical hallmark of this entity.

In conclusion, lymphoma of the lung is extremely rare and is typically of B cell lineage. Non-B cell lymphoma of the lung is an unusual diagnosis and warrants high clinical suspicion. Its presence portends a poor prognosis. To our knowledge, we report the first case of non-HIV related NK/T cell lymphoma with primary lung involvement. Diagnosis is difficult and, because of its aggressive nature, a delay in diagnosis and treatment usually leads to a fatal outcome. It should be included in the differential diagnosis of progressive or unresolved pneumonia, especially when T cell lymphocytosis is persistent in the absence of a well defined infectious aetiology. A definitive diagnosis always requires adequate viable tissues for morphological, immunocytochemical, and



molecular analyses. TBB, transthoracic needle biopsy, and TBNA are generally insufficient and early open lung biopsy or video assisted thoroscopic lung biopsy should be considered. In view of its extreme rarity, there is no recommended treatment at present. CHOP based chemotherapy and surgical resection have been reported in the literature. The response to chemotherapy is variable. Surgical resection may offer a cure in a patient whose tumour is localised. Systemic corticosteroids may be tried as a temporary measure to stabilise the patient sufficiently to undergo surgical biopsy.

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## REFERENCES

- 1 Cadranet J, Wislez M, Antoine M. Primary pulmonary lymphoma. *Eur Respir J* 2002;**20**:750–62.
- 2 Tamura A, Komatsu H, Yanai N, *et al*. Primary pulmonary lymphoma: relationship between clinical features and pathologic findings in 24 cases. The Japan National Chest Hospital Study Group for Lung Cancer. *Jpn J Clin Oncol* 1995;**25**:140–52.
- 3 Asano Y, Ohshima K, Yoshizawa S, *et al*. Modified CHOP in an aged patient with non-Hodgkin's lymphoma and probable extensive pulmonary involvement. *Int J Hematol* 1991;**54**:327–9.
- 4 Boon ES, Graal MB, van Noord JA. Primary extranodal non-Hodgkin's lymphoma of the lung presenting with bilateral, patchy infiltrates dramatically improving after corticosteroid therapy. *Chest* 1993;**104**:1292–3.
- 5 de Torres JP, Kenney L, Celli B. [Primary T-cell pulmonary lymphoma. A case report and review of the literature]. *Arch Bronconeumol* 2002;**38**:596–8.
- 6 Fujihara T, Mori F, Kawano K, *et al*. [A case of T-cell type malignant lymphoma of the lung]. *Nippon Kyobu Geka Gakkai Zasshi* 1993;**41**:258–61.
- 7 Hanada N, Abe T, Katagiri M, *et al*. [A case of T-cell lymphoma showing multiple nodular shadows and an elevated titer of human T-lymphotropic virus type I (HTLV-I) antibody]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1993;**31**:231–4.
- 8 Hanawa T, Chiba W, Fujimoto T, *et al*. [T cell lymphoma presenting as recurrent bilateral pulmonary infiltrates over five years]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1996;**34**:363–8.
- 9 Karakus S, Yalcin S, Guler N, *et al*. Angiocentric T-cell lymphoma of the lung mimicking metastatic carcinoma. Case report. *J Exp Clin Cancer Res* 1998;**17**:371–3.
- 10 Kawashima O, Sakata S, Kamiyoshihara M, *et al*. Primary pulmonary collision tumor including squamous cell carcinoma and T-cell lymphoma. *Lung Cancer* 1999;**23**:67–70.
- 11 Maebara T, Kobayashi H, Kaneko K, *et al*. [A case of T cell lymphoma of the lung]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1991;**29**:469–76.
- 12 Maejima S, Kitano K, Ichikawa S, *et al*. T-cell non-Hodgkin's lymphoma of the lung. *Intern Med* 1993;**32**:403–7.
- 13 Sasaki Y, Yamagishi F, Suzuki K, *et al*. [Primary pulmonary malignant lymphoma of the T-cell type]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1995;**33**:1454–8.
- 14 Greer JP, Kinney MC, Loughran TP Jr. T cell and NK cell lymphoproliferative disorders. *Hematology (Am Soc Hematol Educ Program)* 2001:259–81.
- 15 Kinney MC. The role of morphologic features, phenotype, genotype, and anatomic site in defining extranodal T-cell or NK-cell neoplasms. *Am J Clin Pathol* 1999;**111**:S104–8.

## LUNG ALERT

### Implication of ANCA status in Churg-Strauss syndrome

▲ Sable-Fourtassou R, Cohen P, Mahr A, *et al*. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005;**143**:632–8

Churg-Strauss syndrome is a small vessel vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) in a significant proportion of patients. In this study a cross sectional analysis was performed of the clinical and histological features of patients with Churg-Strauss syndrome in relation to their ANCA status.

A cohort of 112 patients who were enrolled in multicentre treatment trials was selected. They were diagnosed with Churg-Strauss syndrome on the basis of current classifications and were less than 75 years of age. The presence of ANCA was detected by indirect immunofluorescence in 43 patients (38%), 39 of whom had ANCA of the perinuclear type (p-ANCA).

Patients with ANCA had a higher frequency of renal involvement (35% *v* 4%) and peripheral neuropathy (84% *v* 65%) than those without ANCA. In addition, vasculitis was more often observed in the biopsy specimens of the ANCA positive patients (79% *v* 39%). On the other hand, patients without ANCA were more likely to have fever (55% *v* 30%) and cardiac disease (49% *v* 12%). One limitation of the study was that patients who were initially ANCA negative were not retested.

The authors hypothesise the presence of two phenotypes of Churg-Strauss syndrome on the basis of the ANCA status. They conclude that the latter reflects the underlying pathophysiology of the disease, with the presence of ANCA favouring the likelihood of a vasculitis affecting certain organs. Further work is required to determine what effect these findings might have on treatment.

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