



## CASE REPORT

# Chylothorax associated with non-endemic Kaposi's sarcoma

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Chylothorax is a rare cause of pleural effusion, seen in approximately 2% of cases. In HIV-positive patients with Kaposi's sarcoma (KS), the development of chylothorax presents as a diagnostic challenge with an aggressive course and poor, often lethal outcome. In this clinical scenario, the aetiology of chylothorax may include infections and malignancy, while pleural fluid examination and computed tomography of the mediastinum may fail to establish a cause. We present a case of KS-associated non-traumatic chylothorax resulting in death, and a review of available literature on this condition.

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In HIV-positive patients with Kaposi's sarcoma (KS), chylothorax is a rare complication. KS is related to human herpesvirus-8 (HHV-8), and striking reductions in incidence and improvements in survival have been reported after the introduction of highly active antiretroviral therapy (HAART).<sup>[1]</sup> With prolonged survival, the sequelae as well as related complications of KS pleural effusions are increasingly being noted. However, in settings of high tuberculosis (TB) prevalence and limited clinical resources, patients with pleural effusions are typically treated empirically for TB, often with little consideration for KS. The limited availability of diagnostic testing in many settings to investigate unresolving pleural effusion despite TB treatment often presents a diagnostic dilemma. Chylous pleural effusion is an uncommon complication secondary to pathology of the thoracic duct; however, determining the aetiology of chylothorax in HIV-positive patients with KS and/or TB is a significant challenge. The contribution of infectious, malignant and iatrogenic causes needs to be investigated to determine the appropriate management strategy.

## Case

A 40-year-old man sought medical attention for shortness of breath on mild exertion with dry cough of 1 month's duration. He had no significant past medical, social or family history. Physical examination revealed dullness to percussion at both bases, but no significant lymphadenopathy. A chest X-ray revealed bilateral pleural effusion without any infiltration. His sputum was negative twice for acid-fast bacilli (AFB). He tested positive for HIV with a CD4<sup>+</sup> count of 119 cells/ $\mu$ l (6%). He was started on emtricitabine, tenofovir and efavirenz as a fixed-dose combination, *Pneumocystis jirovecii* prophylaxis, and 6 months of standard treatment for pulmonary TB.

After 2 months of this therapy, he reported with violaceous lesions on both legs and his chest wall. Skin biopsy revealed KS and he completed 6 cycles of chemotherapy with doxorubicin, bleomycin and vincristine.

After 6 months of ART, he was virologically suppressed; however, he had immunological failure with a CD4<sup>+</sup> count of 41 cells/ $\mu$ l (5%). Shortness of breath responded to this therapy, but he had radiological persistence of bilateral pleural effusions (Table 1). Repeated thoracentesis revealed straw-coloured fluid with protein >3 g/dl, and inflammatory cells with a lymphocytic predominance without any atypical cells. Despite multiple attempts, no bacterial pathogens or AFB were isolated from the pleural effusion. His skin lesions decreased in size, but he developed woody oedema of the left leg that responded to lower-hemibody irradiation of 800 cGy in a single fraction. Table 1 presents a summary of the major investigations and findings.

Due to persistent bilateral pleural effusions, the patient received 6 cycles of 150 mg/m<sup>2</sup>/day etoposide (injection) from day 1 through day 3 for treatment of pulmonary KS, with a temporary relief in his cough and shortness of breath. He still required repeated thoracentesis to relieve his episodes of breathlessness. Three months after completion of chemotherapy, he developed a worsened shortness of breath and productive cough. The whitish sputum was negative upon Ziehl-Neelsen smear. Contrast-enhanced computed tomography (CT) of the chest confirmed bilateral pleural effusions with consolidation of the right lower zone of the lung, but no pulmonary nodules, mediastinal or hilar lymphadenopathy (Fig. 1). The patient underwent bilateral intercostal chest drainage, revealing thick brownish fluid (Fig. 2). Sputum and pleural fluid were negative for AFB cultures and *Mycobacterium tuberculosis* polymerase chain reaction (PCR) (GeneXpert), but bacterial cultures from pleural fluid grew *Staphylococcus aureus*. These were identified as methicillin-resistant *S. aureus* (MRSA) and the coverage

**Table 1. Summary: Results of key investigations**

Investigation	Findings
Chest X-ray	<ul style="list-style-type: none"> <li>Bilateral pleural effusion without any infiltration</li> </ul>
CT of the chest	<ul style="list-style-type: none"> <li>Bilateral pleural effusion with consolidation of the right lower zone of the lung without any pulmonary nodules or lymphadenopathy</li> </ul>
Sputum examination	<ul style="list-style-type: none"> <li>Negative Ziehl-Neelsen stain (x 2)</li> <li>Negative GeneXpert PCR for <i>Mycobacterium tuberculosis</i></li> </ul>
Pleural fluid examination	<ul style="list-style-type: none"> <li>Straw-coloured</li> <li>Triglycerides 3.1 mmol/l, protein 2.2 g/dl, cholesterol 0.1 mmol/l and LDH 1 344 mol/l</li> <li>Inflammatory cells with a lymphocytic predominance without any atypical cells</li> <li>Cultures negative for bacterial pathogens or AFB</li> </ul>

CT = computed tomography; PCR = polymerase chain reaction; LDH = lactate dehydrogenase; AFB = acid-fast bacilli.

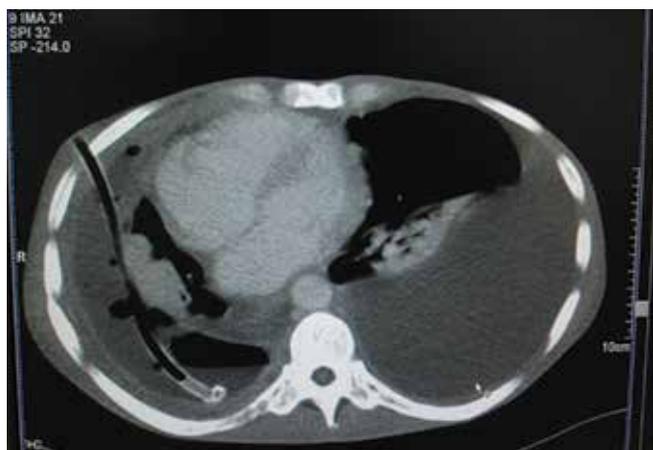


Fig. 1. Computed tomography scan of the chest showing bilateral pleural effusions with consolidation of the right lower zone of the lung with thickened pleura and intercostal drainage tube in place. No significant pulmonary nodules or lymphadenopathy are visible.



Fig. 2. Chest X-ray posteroanterior view showing bilateral pleural effusions with intercostal drainage tube in place.

was narrowed down to vancomycin only. After 5 days of vancomycin therapy, pleural fluid draining from both sides turned milky white in colour. The fluid triglyceride level was 3.1 mmol/l (247 g/dl), protein was 2.2 g/dl, cholesterol was 0.1 mmol/l and lactate dehydrogenase (LDH) was 1 344 mol/l. The patient was diagnosed with bilateral chylothorax and underwent blind pleural biopsy to rule out other aetiologies of persistent bilateral pleural effusion aside from KS-induced scarring of the thoracic duct. Diagnostic bronchoscopy revealed normal trachea and bronchi. The respiratory mucosa was inflamed and red, but visibly normal with no evidence of endobronchial lesions. There were profuse, whitish secretions in the trachea-bronchial tree, which were washed out and sent for microscopy, culture and sensitivity, as well as TB and fungal investigations. Bilateral thoracoscopy revealed empyema with loculations with beefy, inflamed, thick-walled visceral and parietal pleurae. In the presence of low CD4<sup>+</sup> counts, this was regarded as a relapse of pulmonary TB, and anti-tubercular treatment was started. The patient developed sepsis from extended spectrum  $\beta$ -lactamase (ESBL) gram-negative bacteria and died after several days in the intensive care unit.

## Discussion

This patient was diagnosed with HIV with non-endemic KS and pulmonary TB manifesting as bilateral pleural effusion with *S. aureus*

empyema with bilateral chylothorax. Bilateral pleural effusions persisted even after empirical anti-tubercular treatment for 6 months. The presence of advanced HIV disease, pulmonary TB and disseminated KS synchronously posed a difficult diagnostic scenario, and the aetiology of bilateral chylothorax in this patient was unclear. In the setting of HIV-associated KS, the underlying aetiology for bilateral chylothorax may include primary tumour (KS with involvement of pleura or thoracic nodes), infections (related to immunocompromised status and multi-agent chemotherapy) or an unrelated aetiology. Diagnostic bronchoscopy revealed no evidence of endobronchial lesions and ruled out pleuropulmonary KS as the cause for chylothorax.

Chyle consists of lymph of intestinal origin, which is a milky and opalescent fluid rich in lymphocytes, protein, triglycerides and chylomicrons. Chyle is conducted from intestinal lymphatics to the cisterna chyli, which eventually drains into the left subclavian vein via the thoracic duct through the posterior mediastinum. Disruption of flow in the thoracic duct results in mediastinal collection of chyle, which can leak into the pleural space resulting in chylothorax. This manifests as shortness of breath and chest discomfort due to compression of the lung by the collection of chyle. Drainage of milky-white pleural fluid suggests chylothorax that can be confirmed by pleural fluid examination. A level of pleural fluid triglycerides >110 mg/dl and a pleural fluid/serum cholesterol ratio <1 is diagnostic of chylothorax.<sup>[2]</sup> Normally, the

average flow of chyle is about 2 l/day; following meals it may increase to a rate of 4 l/day.<sup>[3]</sup> Continued loss of chyle leads to depletion of protein, fat and lymphocytes. The four main causes of chylothorax include: malignancy; trauma; idiopathic; and miscellaneous causes such as thrombosis of the superior vena cava or subclavian vein, cirrhosis and rarely, pulmonary lymphangiomyomatosis.<sup>[4]</sup>

KS is one of the most common causes of pleural effusion in patients with AIDS. The pathological diagnosis of pleural KS requires a characteristic architectural appearance and not a particular neoplastic cell type.<sup>[5]</sup> The sampled fluid (usually serosanguineous or haemorrhagic exudate) is unlikely to contain diagnostic cytological material. Since KS tends to involve only the visceral pleura, closed pleural biopsy is often non-diagnostic and the diagnosis requires thoracoscopy with the characteristic multiple cherry-red to purple appearance of the KS lesions on the visceral pleura.<sup>[6]</sup> In most cases, the clinical picture and the characteristic bronchoscopic appearance of the lesions help to make a presumptive diagnosis and may obviate the need for biopsy.<sup>[7]</sup> A study describing the clinical course and pleural fluid findings in patients with AIDS-associated pleural KS showed that 21/105 (20%) cases had pleuropulmonary KS involvement. Of these, 13 (62%) had pleural effusions and only 2 had chylothorax. Neither cytological examination nor needle biopsy of the parietal pleura was able to establish the diagnosis. At autopsy, patients with pulmonary KS have multiple cherry-red to purple lesions on the visceral, but not on the parietal pleural surface. The reported median survival from KS diagnosis to death was 205 days for patients with pleuropulmonary KS.<sup>[6]</sup> In another series, 29/53 (55%) patients had pleural effusions including 76% bilateral.<sup>[8]</sup>

Currently, the exact aetiology of chylothorax in patients affected by advanced HIV with KS is unclear, and few cases have been described in the literature.<sup>[8-10]</sup> Most cases reported evidence of lymphatic obstruction via KS involvement of the mediastinal nodes and/or prominent pulmonary KS, and the treatment included palliative measures such as pleural drainage, pleural sclerosis, fluid shunting and/or chemotherapy directed at KS. The treatment was largely unsuccessful, and patients in whom the outcome was noted, died within a few weeks to months. Average survival after diagnosis of KS pleural disease is around 4 months.<sup>[6]</sup> The potential cause of chylothorax in HIV-positive patients also includes TB, but chylothorax appears to be rare in patients with TB, and KS remains the leading concern in the differential diagnosis.<sup>[11]</sup> Chylothorax is also rare in patients with KS without HIV infection (endemic KS) and only a single case of KS-related chylothorax in an HIV-negative patient was reported in past years.<sup>[12]</sup> The pathogenesis of most effusions due to malignancy has been attributed to blockage of the lymphatic drainage system located in the parietal pleura, but this is unlikely in patients with KS-related pleural effusions, since their parietal pleura is not involved. The KS-related effusion may be due to the elaboration of vascular endothelial growth factor (VEGF). VEGF promotes angiogenesis and microvascular hyper-permeability to produce extravascular fluid that appears bloody.<sup>[13]</sup> In patients with KS, the pleural effusion is a chylothorax in about 2% of cases, which suggests involvement of the thoracic duct by the tumour. KS-related chylothorax is postulated to develop from metastases to the thoracic duct. More recently, however, it was demonstrated by the co-expression of HHV-8, CD34 and D2-40 on lesional cells, that chylothorax may arise due to the development of *in situ* KS in this region.<sup>[14]</sup>

The patient described here had no clinical, radiological or cytological indication of pleuropulmonary KS. There was no mediastinal lymphadenopathy, nor any history of chest trauma. Thus, the aetiopathogenesis of his bilateral chylothorax was not clinically or radiologically evident. In this scenario, the reason for chylothorax appeared to be involvement of the thoracic duct by KS, leading to obstruction and a resultant leakage of chyle from the thoracic duct. The process might have been exacerbated by post-chemotherapy fibrosis of mediastinal nodes and/or lymphatic involvement by mycobacteria. This can be evaluated by radioisotope lymphangiography, magnetic resonance imaging or positron emission tomography; however, these investigations are unfortunately not widely available. Further, thoracoscopy with biopsy of mediastinal nodes and a visceral pleural biopsy may help to differentiate KS from TB as the underlying aetiology.

Patients immunocompromised by HIV infection and chemotherapy are at high risk for infection-related effusions. A concomitant infection must be ruled out in patients with KS-related pleural effusion, as a failure to treat a concomitant infection carries a high short-term mortality. In this patient, isolation of MRSA from pleural fluid was probably related to pleurocentesis-related iatrogenic empyema.

## Conclusion

KS-associated chylothorax may present a diagnostic challenge and carries a poor prognosis. Current literature is sparse and a congregation of such cases can provide more insight into the aetiopathogenesis of non-endemic KS-related chylothorax.

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