Clinical Case Reports International

Case Report
Published: 10 Jul, 2017

An Aggressive Small Round Blue Malignancy in the Intensive Care Unit

Loh CH, Tan SH and Tee KH*

Department of Respiratory & Critical Care Medicine, Changi General Hospital, Singapore

Abstract

Ewing sarcoma family of tumors is highly aggressive, with common local recurrence and distant metastases. Histologically they appear as small round blue cells, but this is nonspecific with broad differentials. The ESWR1 break-apart rearrangement using fluorescence in-situ hybridization is pathognomonic for Ewing's sarcoma. Patients with extra skeletal Ewing sarcoma family have a poor prognosis, with median survival ranging between 8 to 15 months in two different case series. Among patients with cancer, approximately 5% develop a critical illness requiring intensive care unit (ICU) admission. We report a case of a young female who developed acute respiratory failure secondary to this rare malignancy that required intensive care treatment. Unlike other reported cases, our patient had a large lung and mediastinal mass with pleura but no bony involvement, associated massive pleural effusion necessitating chest tube insertion, subsequent intensive care admission with invasive ventilatory support. This case highlights the importance of supportive intensive care needed to treat this aggressive disease mainly affecting children and young adults.

Introduction

Cancer patients who require treatment in the intensive care unit (ICU) is growing. In a large retrospective observational study using cancer registry data in the United Kingdom, 5% of cancer patients developed a critical illness and were admitted to an ICU within 2 years of cancer diagnosis [1]. A multicenter study in Brazil found that sepsis and respiratory failure accounted for 15% and 10% respectively of ICU admissions in cancer patients [2].

Sarcomas are a rare group of malignant connective tissue tumors that make up approximately 1% of all adult malignancies [3]. In a retrospective study involving 212 patients over 8 years, the most common sarcoma subgroups admitted to the ICU were unclassified high-grade sarcoma (25%), bone sarcoma (Ewing sarcoma, osteosarcoma, and chondrosarcoma; 17.4%), vascular sarcoma (angiosarcoma and epithelioid hemangioendothelioma; 9.9%), and leiomyosarcoma (7.6%) [4].

Extra skeletal Ewing Sarcoma presenting as a large left sided lung/mediastinal mass requiring intensive care had not been described. We report a unique case of a young female who developed acute respiratory failure secondary to this rare malignancy that required intensive care treatment.

Case Presentation

This was a 30-year-old Indonesian female who was admitted in our hospital, a large tertiary hospital in Singapore. She was a non-smoker/non-drinker with no known past medical history and had no family history of malignancy, tuberculosis, or autoimmune disorder. She presented with dry cough for a month, associated with worsening shortness of breath and left sided pleuritic chest pain. This was accompanied by a loss of appetite and weight over the past 3 weeks.

On examination, she was tachypneic and lethargic, temperature 36.8°C, blood pressure 113/65 mmHg, heart rate 97 per minute, pulse oximetry reading 98% on supplemental oxygen at 2 L/min. There were reduced breath sounds in the left lung, and no lymph nodes or breast lumps were palpable.

She had opacification of the left hemithorax with contralateral trachea shift on erect chest radiograph (Figure 1), with massive pleural effusion found on ultrasound. A chest tube was placed which drained 1350 ml of hemoserous fluid. The pleural fluid was exudative by Light's criteria and lymphocytic (80%) on analysis. Fluid lactate de hydrogenase (LDH) was elevated at 962 U/L and fluid pH was 7.32. Fluid acid fast bacilli smear was negative and no growth was obtained from fluid bacterial cultures.

OPEN ACCESS

Correspondence:

Loh CH, Department of Respiratory & Critical Care Medicine, Changi General Hospital, 2 Simei Street, 529889, Singapore,

E-mail: chee_hong_loh@cgh.com.sg

Received Date: *28 Apr 2017*

Accepted Date: *03 Jul 2017*

Published Date: *10 Jul 2017*

Citation:

Loh CH, Tan SH, Tee KH. An Aggressive Small Round Blue Malignancy in the Intensive Care Unit. Clin Case Rep Int. 2017; 1: 1008.

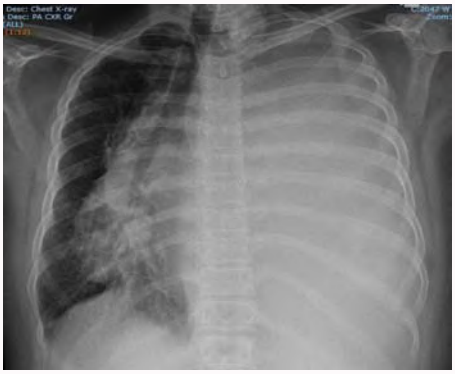

Figure 1: Postero anterior chest X-ray showing opacification of the left hemithorax with contralateral trachea shift.

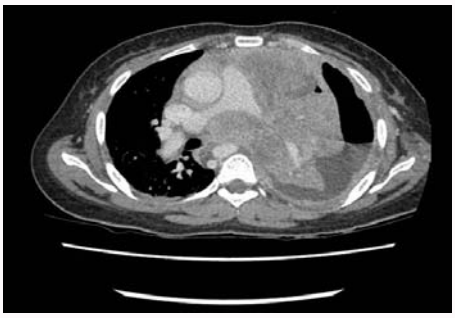

Figure 2: Computed tomography of the thorax showing a large heterogeneous mass in the left hemithorax and mediastinum.

Computed tomography of the thorax, abdomen and pelvis (Figure 2) showed a large heterogeneous mass in the left hemithorax and mediastinum, encasing the left main bronchus causing collapse of the left lung. There was a filling defect in the left main pulmonary artery, which was also encased by tumor. Extensive nodular pleural thickening in the left hemithorax was present, inseparable from the mass. There was also a moderate sized pericardial effusion. No bony erosions were identified. Enlarged upper left para-aortic nodes were noted with a short axis diameter of 1.6 cm. An ill-defined hypodense lesion was noted in the segment IVB of the liver measuring 1.8 cm × 1.4 cm. No enhancing cerebral masses were noted on subsequent contrasted computed tomography of the brain.

She underwent a radiological-guided lung biopsy. The specimen was fixed in 10% neutral formalin and embedded in paraffin. Sections (4-micron thick) were cut and stained with hematoxylin-eosin and periodic acid-schiff (PAS).

The core biopsy showed sheets of small, round, and blue cells (Figure 3), divided into irregular lobules by fibrous stroma. The tumor cells possessed scant cytoplasm and small nucleoli. At least two rosette-like formations were identified. Some rounded globule material in the cytoplasm was highlighted by the PAS stain.

Immunohistochemical studies using commercial antibodies listed in Table 1 was performed. Protocols recommended by the manufacturers were used. Appropriate positive and negative controls were included. The tumor appeared to be diffusely positive with CD99 (Figure 4), and was positive for CD56. The tumor cells were negative for AE1/3, CAM5.2, EMA, (CD45)LCA, CD79A, CD3, CD20, TdT, TTF-1, S100, Desmin, Synaptophysin, Chromogranin and ALK-1, which negate the differential diagnosis of an epithelial/

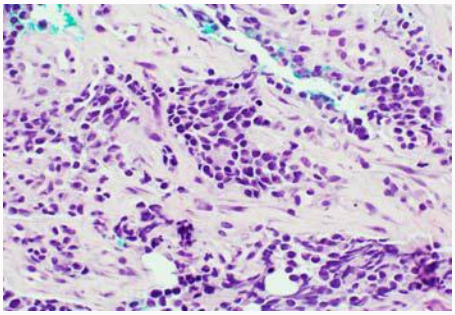

Figure 3: Hematoxylin & Eosin (X400) – The core biopsy showed irregular lobules of 'small round blue cells' with a rosette-like formation in the middle of the field.

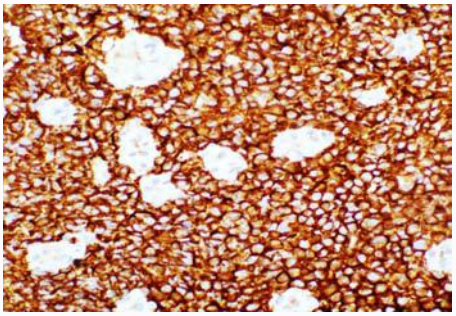

Figure 4: The tumour demonstrated diffuse positivity with CD99 (X400).

neuroendocrine carcinoma, lymphoma, and other 'small round blue cell tumors' such as synovial sarcoma, desmoplastic small round cell tumors and rhabdomyosarcoma. The ki-67 proliferation index was high (around 10% to 15%).

A fluorescence in situ (FISH) study for EWSR1 (EWS RNA-binding protein 1) gene rearrangement with a break-apart 22q12 probe (test developed by the Cytogenetics Laboratory, Department of Pathology, Singapore General Hospital) was performed. These dual-color fluorescent labeled probes hybridize the telomeric and centromeric flanking regions of EWSR1. Where fusion signals exist, no break apart is present. Cells with split signals are considered positive for the ESWR1 break-apart rearrangement, which is present in this case [5]. These findings were pathognomonic for Ewing's sarcoma in this context.

During her admission, she was later noted to be drowsy and found to be hypercapnic. She was intubated for type 2 respiratory failure and mechanically ventilated in the intensive care unit. Repeat chest radiograph showed a new right lower zone consolidation, so she was started on intravenous meropenem for hospital acquired pneumonia.

She was consequently initiated on chemotherapy with Vincristine, Doxorubicin, Cyclophosphamide, and received granulocyte-colony stimulating factor post-chemotherapy. Her hospital course was complicated by diarrhea secondary to *Clostridium difficile* infection. This eventually resolved, and she was transferred back to her home country to continue further chemotherapy. Unfortunately, she was lost to follow up since then.

Discussion

This case report highlights the challenges managing a rare aggressive tumor in a young female patient.

Table 1: Antibodies used for the characterisation of the small round blue cell tumour.

Antigen	Source*	Product Code	Clone	Antigen Retrieval Method
AE1/3	DAKO	M3515	AE1 and AE3	Enzyme
CD3	NOVOCASTRA	NCL-L-CD3-565	LN10	HIER
CD5	NOVOCASTRA	NCL-L-CD5-4C7	4C7	HIER
CD20	DAKO	M0755	L26	HIER
CD45	DAKO	M0701	2B11+PD7/26	HIER
CD56	NOVOCASTRA	PA0191	CD564	HIER
CD79a	DAKO	M7050	JCB117	HIER
CK19	DAKO	M0888	RCK108	HIER
Chromogranin A	DAKO	M0869	DAK-A3	HIER
Desmin	DAKO	M0760	D33	HIER
EMA	DAKO	M0613	E29	HIER
Ki67	DAKO	M7240	MIB1	HIER
P16	Ventana	705-4713	E6H4	HIER
S100	DAKO	Z0311	Polyclonal	Enzyme
Synaptophysin	NOVOCASTRA	NCL-L-SYNAP-299	27G12	HIER
TdT	NOVOCASTRA	NCL-L-TdT-339	SEN28	HIER
TTF-1	NOVOCASTRA	NCL-L-TTF-1	SPT24	HIER
EBER-ISH	NOVOCASTRA	AR0833	N.A	Enzyme
CD99	NOVOCASTRA	NCL-CD99	H036-1.1	HIER
ALK	Ventana	790-4794	D5F3	HIER

EMA: Epithelial Membrane Antigen; TDT: Terminal Deoxynucleotidyl Transferase; TTF-1: Thyroid Transcription Factor-1; EBER-ISH: Epstein–Barr Virus-Encoded Small RNAs-Insitu Hybridisation; ALK: Anaplastic Lymphoma Kinase; HIER: Heat-Induced Epitope Retrieval. *Sources were as follows: Dako: Dako Denmark A/S, Glostrup, Denmark; Novocastra: Novocastra, Leica Biosystems Newcastle Ltd, Newcastle, United Kingdom; Ventana: Ventana Medical Systems Inc, Arizona, USA.

Small blue round cell tumors have a typical clear cytoplasm on hematoxylin and eosin staining, due to the presence of glycogen. The differentials of small round blue cell tumors are broad, including Ewing sarcoma family, lymphoma, small-cell osteosarcoma, mesenchymal chondrosarcoma, dedifferentiated synovial sarcoma, desmoplastic small round cell tumors and rhabdomyosarcoma [6].

In 1979, Askin et al. [7] described an aggressive primitive neuro ectodermal tumor (PNET) of the thoracopulmonary region primarily involving children and young adults. The most common radiographic manifestation is a chest wall soft-tissue density mass, sometimes associated with rib erosion with or without pleural effusion [8]. Over the past decades, the Ewing sarcoma family of tumors is classified according to their histologic appearance from undifferentiated Ewing sarcoma (ES), to atypical poorly differentiated ES and differentiated PNET.

In the 2013 World Health Organization classification of tumors of soft tissue and bone [9], the term PNET was removed to minimize confusion with the histologically and genetically different PNET of the central nervous system and female genital tract.

The Ewing sarcoma family of tumors (ESFT) share similar immunohistochemistry, and is positive for MIC2 surface antigen (CD99 gene). Cytogenetically, the translocation t (11, 22) (q24; q12) is pathognomonic, occurs in 85% of cases and gives rise to the formation of the EWS-FLI 1 fusion gene which is detected by FISH.

A Korean case series of 70 patients studied over 17 years reported the characteristics of extra skeletal Ewing sarcoma. Most primary tumors manifested as large and bulky soft-tissue masses (mean size, 9.0 cm; range, 1.3 cm to 23.0 cm), frequently invading adjacent organs (45.6%) and showed heterogeneous enhancement (73.7%), a well-defined (66.7%) margin, and partial necrosis or cystic degeneration (81.9%). Metastasis was most frequent to lymph nodes (75.9%), followed by bone (31.0%), lung (20.7%), abdominal solid organs (13.8%), peritoneum (13.8%), pleura (6.9%), and brain (3.4%) [10].

Ewing sarcoma family of tumors is highly aggressive, with common local recurrence and distant metastases. The American Joint Committee on Cancer (AJCC) tumor, node and metastases (TMN) staging systems [11] for primary tumors of bone and soft tissue sarcoma are not widely used for Ewing family of tumors, but are sometimes used for staging of Askin's tumors. Using the AJCC TNM staging system for soft tissue sarcoma [11], our patient would be classified to have T2b (deep tumor/mediastinal involvement), likely N1 (involvement of para-aortic and axillary regional nodes), and M1 with possible liver metastasis, consistent with stage III disease, stage IV if histologically confirmed distant spread. tumors that arise outside skin or subcutaneous sites have a worse prognosis [12]. Standard guidelines are absent for the treatment of Askin's tumors. However the main stay of treatment based on case series includes neo adjuvant chemotherapy, surgical resection [13] and adjuvant chemotherapy and radiotherapy [13].

The median survival in Askin's first case series [7] was 8 months. A Chinese case series of 11 patients (mean age 14.5 years old, range 8-22 years old) with Askin tumor found that the median survival for combined (chemotherapy-surgery-radiotherapy) treatment was 15 months. Poor prognosis was associated with tumor diameter >5 cm, LDH levels >240 U/l and late stage (stage III or IV) tumors [14].

The overall survival in sarcoma in the ICU is comparable with

other critically ill patients with other solid tumors [15]. However, among patients with multiple organ failures, cancer patients had higher mortality rates than non-cancer patients [4]. In a retrospective study performed in a large cancer hospital in the United States, the mortality rate for sarcoma in the ICU was 23% (95%CI, 16.9% to 29.6%), which rose to 59% at six months [4]. Acute respiratory failure is the most common cause of ICU admission in cancer patients, and often leads to mechanical ventilation, however, survival remains poor [16].

Unlike other reported cases, our patient had a large lung and mediastinal mass with pleura but no bony involvement, associated massive pleural effusion necessitating chest tube insertion, intensive care admission with invasive ventilatory support. This case highlights the importance of supportive intensive care needed to treat this aggressive disease mainly affecting children and young adults. In young patients with expected good lung reserve, respiratory symptoms may manifest late in the natural progression of Askin tumors without external chest wall signs. Careful respiratory examination followed by an initial chest radiograph can possibly detect this devastating tumor at an earlier stage.

References

1. Puxty K, McLoone P, Quasim T, Sloan B, Kinsella J, Morrison DS. Risk of critical illness among patients with solid cancers: A population-based observational study. JAMA Oncol. 2015;1(8):1075-85.
2. Soares M, Caruso P, Silva E, Teles JM, Lobo SM, Friedman G, et al. Characteristics and outcomes of patients with cancer requiring admission to intensive care units: a prospective multicenter study. Crit Care Med. 2010;38(1):9-15.
3. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC cancer staging manual. Springer Science, Business Media, LLC. 2017.
4. Gupta R, Heshami N, Jay C, Ramesh N, Song J, Lei X, et al. Predictors of survival in patients with sarcoma admitted to the intensive care unit. Clin Sarcoma Res. 2016;6(1):12.
5. Cerrone M, Cantile M, Collina F, Marra L, Liguori G, Franco R, et al. Molecular strategies for detecting chromosomal translocations in soft tissue tumors (review). Int J Mol Med. 2014;33(6):1379-91.
6. Benbrahim Z, Arifi S, Daoudi K, Serraj M, Amara B, Benjelloun MC, et al. Askin's tumor: a case report and literature review. World J Surg Oncol. 2013;11(1):10.
7. Askin FB, Rosai J, Sibley RK, Dehner LP, McAlister WH. Malignant small cell tumor of the thoracopulmonary region in childhood. A distinctive clinicopathologic entity of uncertain histogenesis. Cancer. 1979;43(6):2438-51.
8. Sabati JM, Franquet T, Parellada JA, Monill JM, Oliva E. Malignant neuroectodermal tumour of the chest wall (Askin tumour): CT and MR findings in eight patients. Clin Radiol. 1994;49(9):634-8.
9. Fletcher CMD, Bridge JA, Hogendoorn PCW, Mertens F. WHO classification of tumours of soft tissue and bone. In: World Health Organisation classification of tumours. Lyon: International Agency for Research on Cancer. 2013.
10. Huh J, Kim KW, Park SJ, Kim HJ, Lee JS, Ha HK, et al. Imaging features of primary tumors and metastatic patterns of the extraskeletal ewing sarcoma family of tumors in adults: A 17-year experience at a single institution. Korean Radiol. 2015;16(4):783-90.
11. AJCC cancer staging manual. New York: Springer-Verlag Inc, USA; 2010.
12. Orr WS, Denbo JW, Billups CA, Wu J, Navid F, Rao BN, et al. Analysis of prognostic factors in extraosseous Ewing sarcoma family of tumors: review of St. Jude Children's Research Hospital experience. Ann Surg Oncol. 2012;19(12):3816-22.
13. Christiansen S, Semik M, Dockhorn-Dworniczak B, Rötker J, Thomas M, Schmidt C, et al. Diagnosis, treatment and outcome of patients with Askin-tumors. Thorac Cardiovasc Surg. 2000;48(5):311-5.
14. Zhang KE, Lu R, Zhang P, Shen S, Li X. Askin 's tumor : 11 cases and a review of the literature. Oncol Lett. 2016;11(1):253-6.
15. Taccone FS, Artigas AA, Sprung CL, Moreno R, Sakr Y, Vincent JL. Characteristics and outcomes of cancer patients in European ICUs. Crit Care. 2009;13(1):R15.
16. Shimabukuro-Vornhagen A, Böll B, Kochanek M, Azoulay É, von Bergwelt-Baildon MS. Critical care of patients with cancer. CA Cancer J Clin. 2016;66(6):496-517.