

Primary oesophageal Ki (CD30)-positive ALK⁺ anaplastic large cell lymphoma of T-cell phenotype

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ABSTRACT

Primary oesophageal lymphoma is a very rare entity, with fewer than 30 reported cases worldwide. It represents an important cause of dysphagia. Most of the oesophageal lymphomas are diffuse large B-cell type, with only one reported case of anaplastic large cell lymphoma (ALCL) of T-cell phenotype. Primary oesophageal lymphomas that are not associated with an immunocompromised state tend to affect elderly patients. We describe the first case of primary oesophageal Ki (CD30)-positive ALK⁺ALCL of T-cell phenotype in a 34-year-old immunocompetent woman, who presented with a two-year history of dysphagia. She was treated with chemotherapy and endoscopic oesophageal dilations and stenting, resulting in complete remission of the lymphoma and resolution of the dysphagia. She then underwent autologous peripheral blood haematopoietic stem cell transplantation and remained disease-free two years after the diagnosis.

KEYWORDS: anaplastic large cell lymphoma, anaplastic lymphoma kinase, dysphagia, Ki (CD30)-positive ALK⁺, lymphoma, primary oesophageal lymphoma

Singapore Med J 2008;49(10):e289-e292

INTRODUCTION

Approximately 98% of oesophageal malignant neoplasms are squamous cell carcinomas, with the remaining being almost exclusively adenocarcinomas.⁽¹⁾ Primary oesophageal non-Hodgkin lymphoma (NHL) is exceedingly rare, with only a few reports of anaplastic large cell lymphoma (ALCL). To the best of our knowledge, there has only been one report of ALCL of T-cell phenotype of the oesophagus in a 73-year-old man, who had received three years of immunosuppressive therapy for Lambert-Eaton syndrome and in which the diagnosis was made postmortem.⁽²⁾ Previously, ALCL was classified as either a subset of T-cell or null cell lineage in the Revised European-American Classification of Lymphoid Neoplasm (REAL),⁽³⁾ and regarded as a high-grade lymphoma according to the working formulation.⁽⁴⁾

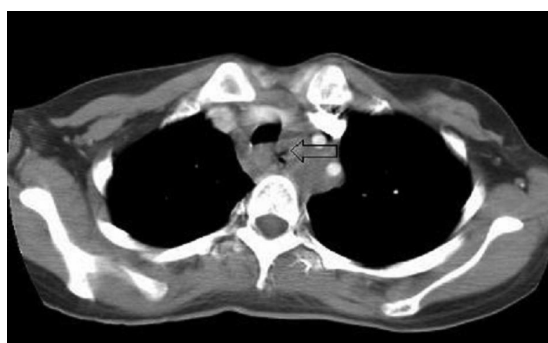


Fig. 1 Axial CT image at presentation shows an eccentric proximal oesophageal wall thickening at the T2 vertebral level with narrow lumen (arrow).

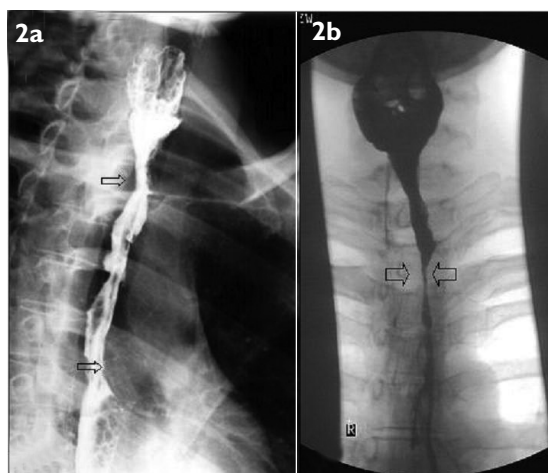


Fig. 2 Barium swallow shows (a) narrowing from the proximal to the middle part of the oesophagus (arrows), and (b) oesophageal stricture at the T2 vertebral level (arrows).

The tumour cells exhibit diffuse positivity for Ki-1 (CD30) and variable expression of anaplastic lymphoma kinase (ALK), but are negative for Leu-M1 (CD15).⁽⁵⁾ ALK⁺ALCL predominantly affects young male patients and, if treated with chemotherapy, has a favourable prognosis. In contrast, ALK⁻ALCL occurs in older patients and has an unfavourable prognosis. ALCL is frequently associated with Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) infection or other immunodeficiency states.⁽⁵⁾ We describe a very rare case of primary oesophageal ALK⁺ALCL in an immunocompetent young woman who responded to chemotherapy.

CASE REPORT

A 34-year-old woman was referred to us for further

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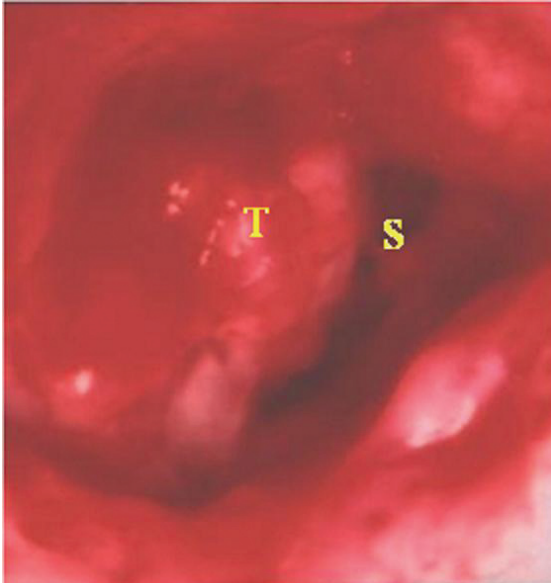


Fig. 3 Endoscopic view at presentation shows a fungating tumour (T) of the upper oesophagus with tight stricture (S).

management of dysphagia. She had difficulty in swallowing solids initially and had intermittent odynophagia over the past one year. There was also hoarseness of voice for the past few months. There was no prior history of corrosive ingestion or instrumentation of the oesophagus.

The physical examination on admission was unremarkable. Indirect laryngoscopy showed a paralysed left vocal cord. The haemoglobin was 10.5 g/dL (normal red cell indices), leucocyte count $8.3 \times 10^9/L$ (normal differential counts) and platelets $540 \times 10^9/L$. The EBV and HIV tests were negative. Computed tomography (CT) at presentation showed dilated proximal oesophagus with an eccentric proximal oesophageal thickening at the T2 vertebrae level with left subclavian vein partially encased within this lesion. No lymphadenopathy or lesion was found elsewhere (Fig. 1). Barium swallow revealed irregular thickening of the oesophageal wall and stricture from the level of C6 to the middle of the oesophagus (Fig. 2), and regurgitation of the contrast into the trachea but no tracheo-oesophageal fistula. Endoscopic examination revealed a hard fungating lesion in the proximal oesophagus at 20 cm from the incisor that bled to the touch. It produced a tight stricture that prevented completion of the endoscopic assessment (Fig. 3).

Histologically, the tumour was composed of large atypical lymphoid cells with extensive eosinophilic and neutrophilic infiltration. The atypical cells were diffusely positive for CD30, ALK and CD45RO, but negative for CK, CD15, CD20 and CD79 α , consistent with ALCL of T-cell phenotype (Fig. 4). Bone marrow

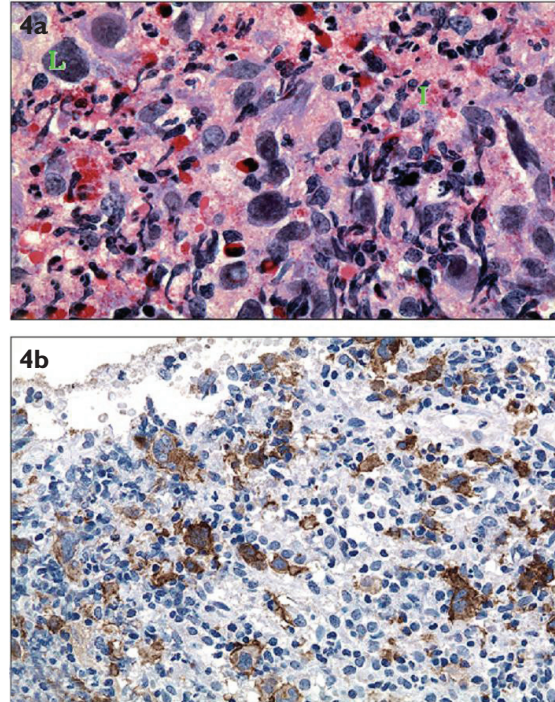


Fig. 4 Photomicrographs of the oesophageal mass show (a) the presence of large tumour cells with hyperchromatic and irregular nuclei, some with prominent nucleoli (L) and extensive eosinophilic and neutrophilic infiltration (I) (Haematoxylin & eosin, $\times 400$); and (b) diffuse positive staining of the large tumour cells for CD30 (CD30, $\times 40$).

biopsy showed marrow infiltration consistent with stage IV disease.

She received modified BFM-90 chemotherapy consisting of vincristine, methotrexate/ifosfamide/cytosine arabinoside/etoposide/dexamethasone given triweekly for three cycles resulting in partial relief of the dysphagia. However, about one month after the last cycle of chemotherapy, she developed worsening dysphagia. Barium swallow and oesophagogastroduodenoscopy findings showed oesophageal stricture associated with fibrosis and no evidence of active disease. She underwent oesophageal dilations and stenting, resulting in a resolution of the dysphagia and then autologous peripheral blood haematopoietic stem cell transplantation (PBSCT). Three years after the onset of dysphagia and two years after the diagnosis, the patient was still alive and free of disease.

DISCUSSION

Gastrointestinal involvement by NHL is common,⁽⁶⁾ especially in the stomach and small intestine. However, oesophageal involvement is uncommon, occurring in approximately 1% of all gastrointestinal lymphoma,⁽³⁾ and in most cases, it is as a result of a local extension from gastric or hilar nodal disease. Identification of the oesophagus as the primary site of lymphoma is

Table I. Clinical profile and pathological findings of reported cases of primary oesophageal non-Hodgkin lymphoma.⁽¹⁹⁾

Patient no.	Age (years)	Gender [†]	Site of tumour [‡]	Gross appearance	Histopathology	Treatment [§]	Clinical outcome after diagnosis
1. ⁽²⁾	30–71	M:4;F:4	U:1,D:7	Nodular:6; submucosal:1; varicoid:1	Histiolytic:4 Lymphocytic:4	R &/or C	1–3 years: 6 alive; 7 years: 1 alive; 1 unknown
2. ⁽³⁾	48	M	D	Polypoid	Histiocytic	R and C	ND
3. ⁽⁴⁾	45	M	D	Varicoid	Centrocyte-type	S	ND
4. ⁽⁵⁾	82	F	M–D	Submucosal	Diffuse large B-cell	S	7 months, dead
5. ⁽⁶⁾	67	M	P	Nodular	Diffuse large B-cell	R & C	14 months, dead
6. ⁽⁶⁾	86	F	D	Submucosal	Moderately differentiated large	S	12 months, dead
7. ⁽⁷⁾	75	F	D	Gelatinous mass	Small lymphocytic B-cell	C	5 years, dead
8. ⁽⁸⁾	60	M	M	Submucosal	Follicular small cleaved B-cell	C	2 years, alive
9. ⁽⁹⁾	77	F	M	Submucosal	T-cell	R & C	7 months, alive
10. ⁽¹⁰⁾	48	M	D	Eccentric Extramucosal	High grade small non-cleaved	ND	6 weeks, dead
11. ⁽¹¹⁾	74	M	ND	Submucosal	Medium-sized non-cleaved B-cell	S & C	4 months, alive
12. ⁽¹²⁾	55	M	M–D	Ulceration	Diffuse intermediate B-cell	C	8 days, dead
13. ⁽¹³⁾	55	M	D	Polypoid	Diffuse large B-cell	S & C	2 years, alive
14. ⁽¹⁴⁾	83	M	D	Protruding	Small lymphocytic	ND	ND
15. ⁽¹⁵⁾	56	M	P	Submucosal	Diffuse large B-cell	C & R	1 year, alive
16. ⁽¹⁶⁾	76	M	M	Lobulated Mucosal mass	Large cell	ND	ND
17. ⁽¹⁷⁾	83	F	M	Submucosal	MALT	S	22 months, alive
18. ⁽¹⁸⁾	52	M	D	Polypoid mass	Diffuse large B-cell	C	14 months, alive
19.*	34	F	P	Submucosal	Anaplastic large T-cell	C & PBSCT	1 year, disease-free

* Current case

† M: male; F: female

‡ P: proximal; M: middle; L: distal

§ R: radiotherapy; C: chemotherapy; S: surgery; PBSCT: peripheral blood haematopoietic stem cell transplantation

ND: not described

MALT: mucosa associated lymphoid tissue

rare. Some of these cases may not represent primary oesophageal lymphoma when judged by criteria set by Dawson et al.⁽⁷⁾ As evident in our patient, it is described as primary oesophageal, when only the oesophagus or the satellite nodes are involved, in the absence of distal lymphadenopathy and involvement of the liver or spleen or other gastrointestinal sites.

Table I summarises the clinical and pathological findings of the reported primary oesophageal lymphoma cases to date.^(2–19) The majority of the patients were above 45 years of age and had mid to lower oesophageal disease. Lesions involving the proximal third of the oesophagus are more likely to present with serious complications,⁽²⁰⁾ including paralysis of the recurrent laryngeal nerve and vocal cord, formation of fistula and stricture, and development of aspiration pneumonia.

There is no typical radiological pattern, and barium studies may mimic carcinoma. Endoscopy findings, which include polypoidal masses, ulceration, large intramural mass, varicoid pattern and multiple

submucous nodules, are not diagnostic. CT of the thorax and abdomen are needed for staging and for evaluation of the tumour mass after chemotherapy. Immunohistochemical studies are mandatory to distinguish lymphoma from carcinoma of the oesophagus and also to differentiate between B- and T-cell subtypes, which differ in treatment and outcome. Majority of the tumours were of the B-cell phenotype, with a few cases of the T-cell phenotype. To the best of our knowledge, there has been only one report concerning primary oesophageal ALCL of T-cell subtype involving the distal oesophagus in an immunocompromised elderly man.⁽²¹⁾ Therefore, our patient is the first case to date, of ALK⁺ALCL arising in the proximal oesophagus in an immunocompetent young woman.

ALK⁺ALCL frequently presents as an aggressive stage III and IV disease with bone marrow involvement in up to 30% of cases.⁽²²⁾ Extranodal involvement is frequent (60%) with the skin being the most frequent

extranodal site.⁽²³⁾ Distinction of ALK⁺ALCL and ALK⁻ALCL is clinically important, because the former shows a more favourable clinical course. ALK⁺ALCL appears to benefit from chemotherapy and showed a far better five-year survival rate (79.8%) than ALK⁻ALCL cases (32.9%).⁽²⁴⁾

Currently, no recommendation regarding standard treatment exists as treatment modalities utilised previously have varied significantly. In the earlier years, surgery was a common choice, but more recently, chemotherapy and radiotherapy have become the preferred modes of therapy. Nonetheless, optimum management of oesophageal lymphoma often requires a multidisciplinary approach; patients may require surgical intervention when complication arises. Chemotherapy is the mainstay of treatment in ALCL. Surgery has been recommended to avoid or treat obstruction, haemorrhage or perforation. Strictures could be treated with endoscopic oesophageal dilatations or stenting.

Our patient received modified BFM-90 chemotherapy protocol every three weekly for three cycles followed by autologous PBSCT, resulting in complete remission of the lymphoma and partial relief of the dysphagia. She also required multiple oesophageal and stenting to relieve the dysphagia. The possible causes of dysphagia in our patient included scarring and stricture of the oesophagus due to firstly, desmoplastic (fibrous) reactions associated with the lymphoma, and secondly, repeated episodes of infection. Autologous PBSCT was performed in view of the high-grade tumour (anaplastic, and T-cell phenotype) and late presentation.

Primary oesophageal lymphoma, although very rare, remains an important differential diagnosis of dysphagia. ALCL should be looked for among young patients with oesophageal tumour. Because the biological and clinical characteristics of primary ALCL of the oesophagus are currently unknown, further study is required before optimal treatment can be recommended.

ACKNOWLEDGEMENTS

We are grateful to Associate Professor Dr Wan Muhaizan WM and Associate Professor Dr Phang KS for the histological photographs, Dr Loi HY and Dr Shahizon MM for the radiological photographs, and Dr Ng SC for his assistance in managing the case.

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