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A CASE REPORT OF A MIXED THYMOMA AND REVIEW OF THE LITERATURE

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ABSTRACT

Considering the universal rarity of neoplasms of the thymus, and the finding that there exists very limited epidemiologic data on the thymomas and thymic carcinoma, it is interesting however that when anterior mediastinal masses are detected and subjected to evaluation, over 50% of them turn out to be thymomas. They exhibit a range of heterogenous clinical and pathological characteristics, such that there are no standardized guidelines yet established for their management or treatment. On this background, we report the case of a mixed thymoma (WHO type AB thymoma) in a 61 year old businessman who had presented with a recurring right-sided chest pain and dyspnoea on exertion, over a six (6) month duration. The final diagnosis was confirmed after an earlier missed diagnosis was encountered; this followed the histological examination of a trans-thoracic trucut biopsy of the tumour which is more to the right of the thorax.

KEYWORDS: Mediastinal mass, Thymoma, Mediastinal tumour.

INTRODUCTION

Thymomas are tumours of the thymus, that derive from the thymic epithelium, or exhibit a differentiation towards thymic epithelial cells.[1,2] They constitute part of an extremely heterogeneous group of neoplasms and exhibit a very wide range of clinical and morphological characteristics.[2,3] A thymoma may be a non-invasive, encapsulated tumour, or an aggressively invading tumour, or can even be variably associated with several types of autoimmune disorders, For example myasthenia gravis, rheumatoid arthritis, scleroderma, hypogammaglobulinaemia, and red cell aplasia.

The aetiology remains largely unknown, although some epidemiologic clusters have associated some thymomas with multiple endocrine neoplasia (MEN-1) syndrome and Epstein-Barr virus infection.[2] They are one of the rarest of human neoplasms, with an annual incidence of approximately 1 to 5 per million population, and there is very limited epidemiologic data reported on thymomas and thymic carcinoma.[1,2] These thymic tumours can occur at almost all ages, with peak incidence seen between 55 and 65 years of age.[2] Symptoms may be due to local complications too, and may include pain, respiratory insufficiency (or dyspnoea), superior vena cava syndrome, and tachycardia.[2]

The major types or histological subtypes of thymoma are the WHO type A and type B, based on the shape of the composite epithelial cells and their nuclei. Type A has neoplastic epithelial cells and nuclei that are spindle or oval shaped, while the type B thymoma has cells (and nuclei) that are predominantly round or polygonal in shape. In this regard, the type B thymoma is sometimes described as epithelioid. Furthermore, a mixed variant or the type AB combines features of the types A and B or B1-like features histologically. Depending on the clinical stage, cure can usually be achieved in some cases by radical surgery (or resection)[3] The types A and AB at clinical stages I and II usually have a favourable clinical course.[3] We report this case on account of the universal rarity of thymoma as a human neoplasm, and also on the basis that, management or treatment guidelines are not yet standardized for this entity. This we hope may trigger the need for further research in this area in the future.

CASE REPORT

The patient was a 61 year old man and trader, who presented with a history of recurrent right sided chest pain and exertional dyspnea, both of 6 months duration. This pain was described as sharp (or acute), constant, not radiating or referred to any other region (or site) of the body. It was not severe enough as to limit or stop his regular activity, and was relieved by analgesics, but has

no known aggravating factors. There was an associated history of shortness of breath (dyspnoea) which worsened with strenuous exertion. There was no history of cough, haemoptysis, or contact with persons infected with tuberculosis. There was no history of orthopnoea or of paroxysmal nocturnal dyspnea.

However, a history of significant weight loss was given, but the patient's appetite was good, and he had no changes in bowel habit. He had no bone pain or jaundice, and he volunteered a history of smoking cigarettes about thirty years ago (but unable to quantify it), and inhales locally prepared snuff (ground tobacco leaves) as well. He is not a hypertensive or asthmatic patient.

The patient had a large right pleural effusion two years prior to the above presentation, which was drained. Details of the fluid cytology are not available.

The physical examination findings were of a middle aged man in mild respiratory distress, but who was afebrile, acyanosed, had no significant lymphadenopathy, nor pedal or leg oedema. The respiratory rate (RR) was 23 cpm (cycles per minute) and percussion notes were dull over the right anterior, and right lateral mid to lower lung zones. On auscultation the breath sounds were reduced over the right lung field, but no crepitations were heard. Cardiovascular system examination revealed a pulse rate (PR) of 92 bpm (regular and full volume), blood pressure of 140/80 mmHg, and only normal S1 and S2 (first and second) heart sounds were heard on auscultation.

The investigation findings came as follows. The chest x-ray showed a large homogenous opacity in the right hemithorax sparing the apex with a tracheal shift to the left. A chest CT scan showed a non-enhancing mixed density mass, occupying most of the right mid to lower hemithorax, measuring 11.4 x 15.9 x 23.2cm, with a small mediastinal component. Flakes of calcification were seen within this mass. The apex of the right lung and the left lung appeared within normal limits. No enlarged mediastinal lymphnodes were seen and there was no pleural effusion. Based on the above preliminary findings, a provisional diagnosis of a bronchogenic carcinoma was made or queried. Total blood counts/ differential tests revealed a PCV (packed cell volume) of 35%, total white cell count of 4.93 x 10^9/L with lymphocytosis, and a relative neutropenia, adequate (or normal) platelet count, and an ESR 31 mm/Hr.

The patient had a right transthoracic trucut lung biopsy procedure done, which showed a hard gritty tumour, with a yellowish appearance on cut section. The histologic examination of the biopsied tissue revealed the features of a mixed thymoma, characterized by a dual population picture. One population is composed of spindle shaped neoplastic thymic epithelial cells in a swirling pattern (WHO type A), and the other population has polygonal shaped or epithelioid cells (WHO type B1).

This is the WHO type AB thymoma (See figures 1, 2, and 3 below showing these cell types or population described).

The diagnosis and treatment options were explained to the patient, and he opted for the following plan, although he was earlier hesitant and refused surgery. For neo-adjuvant chemotherapy he was referred to the Oncology clinic. Thereafter, he was to have CT scans to re-stage the tumor, sternotomy/thoracotomy with thymectomy plus tumour ablation if feasible, and possible post-operative radiotherapy. He commenced chemotherapy. After taking three courses of chemotherapy, the patient became more frail, and could not stand surgery, although there was some degree of poor therapeutic compliance, and he died even before the other treatment options could be instituted. The patient's demise was about a year and a half following the commencement of his index management.

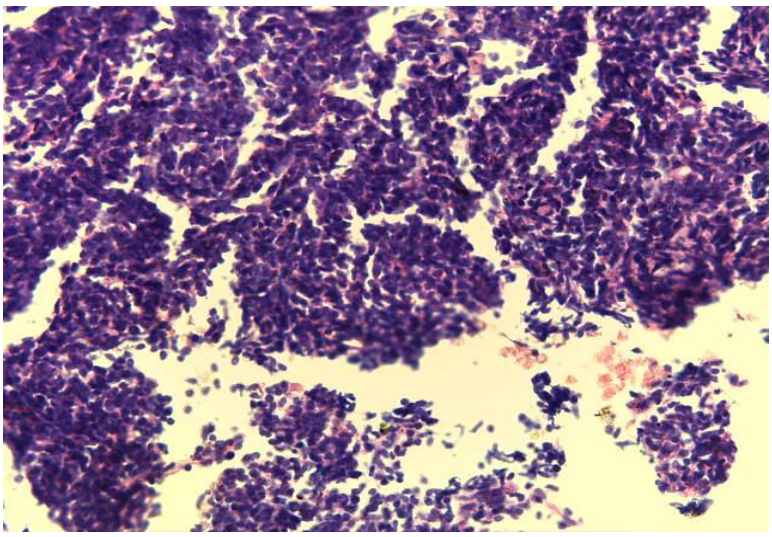

Fig. 1: Histological section shows sheets and nests of polygonal shaped or epithelioid neoplastic thymic epithelial cells. *Obj. X10, H & E Stain.*

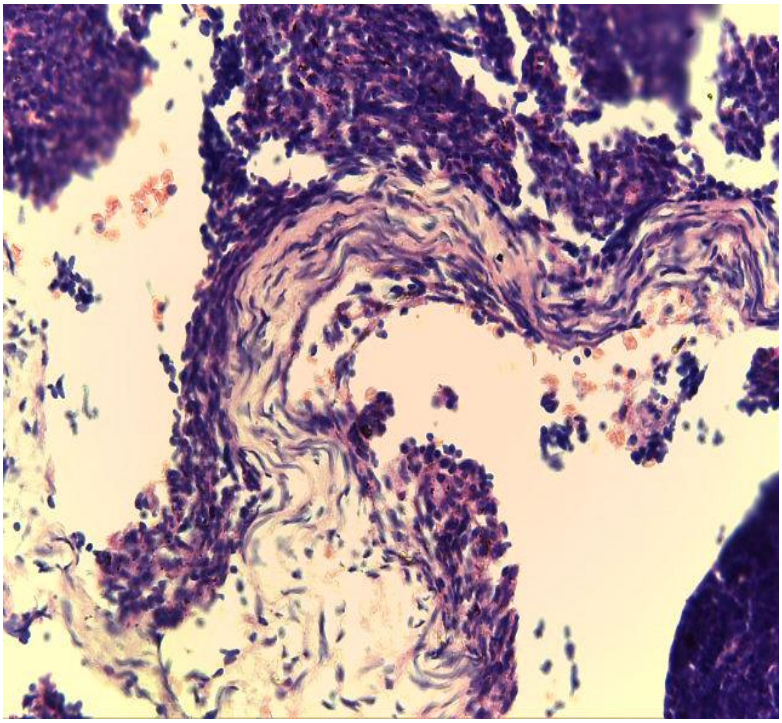

Fig. 2: On this section, few lymphocytic cells are admixed with a spindling fibroblastic stroma in a background of a thymoma tissue. ***Obj X 10, H & E Stain.***

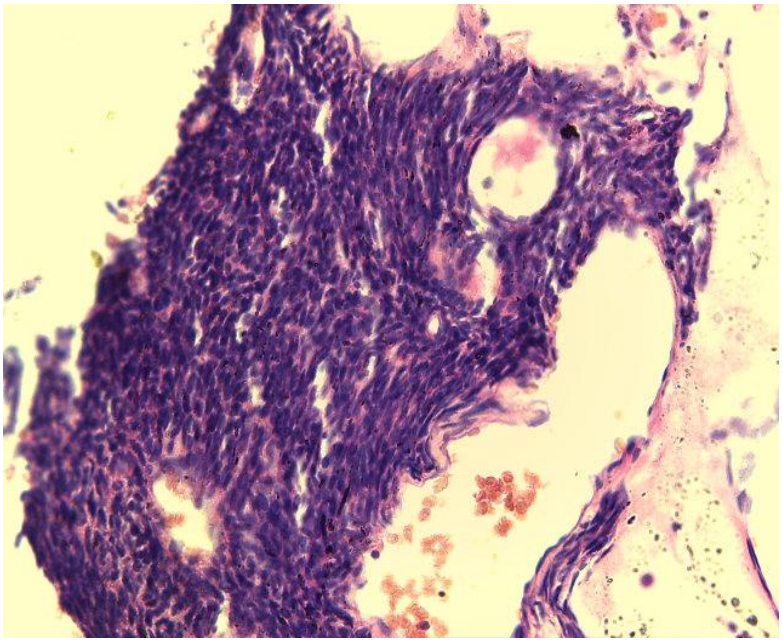

Fig. 3: Histological section showing some polygonal shaped neoplastic cells (left third of the field) admixed with a predominant population of spindle shaped neoplastic thymic epithelial cells (right two thirds of field). Features of a mixed (WHO type AB) thymoma. ***Obj. X 10, H & E Stain*****.**

DISCUSSION

The general or universal rarity of the thymomas and thymic neoplasms makes it an interesting curiosity when a case is encountered, as they are also an extremely heterogenous group of neoplasms lacking a standardized or established management guidelines.[1,2,6] A study on their trends and incidence in the USA population (Hsu et al[1]) has confirmed this rarity, with a concomitant decline in the incidence rates of thymomas, as compared to thymic carcinoma. A wide age range of patients can be affected by the thymomas, but peak incidence is usually seen in the 7th decade of life, with males and females being nearly equally affected.[2,4] The clinical diagnosis is usually based on an association, in some cases with presence of myasthenia gravis symptoms and other autoimmune paraneoplastic syndromes, like hypogammaglobulinaemia and red cell aplasia.[2-4,7] (See table 1 below).

Table 1: Literature Review on Thymoma Cases Reported.

S/N	Author/year	Patients age (years)	Sex/gender	Symptoms	Diagnosis	Treatment/ management	Outcome, recurrence and prognosis
1	Karras[11]… 2005	Range of 49±14yrs	21 patients, M:F ratio 8:13	Symptoms of MG, SLE & pure red cell aplasia	WHO types AB and B2 (or high grade malignant thymoma) were most common	Surgery was curative	Nephrotic syndr in 75%, renal failure in 50%, 38% died from thymoma and 17% developed end stage renal failure
2	Mori[14] …2007	3 cases, 69 (M) 74 (M) 46 (M)	All males	Multiple tumours in all, MG symptoms in all	Type B2, A and B1 thymomas	Surgery, Radiotherapy in patient 2	Complete remission in all patients
3.	Harnath[7]… 2012	Median age 50.6	93 patients, Men and women almost equally affected, Slight male predominanc	Median tumour size 8.5cm, Symptoms are dyspnoea, chest constriction and pain, cough MG symptoms	WHO types A,AB, B1,B2,B3 and thymic carcinoma	Surgery, Post-op radiation	33.3% of patients relapsed after a median period, 5.6yrs. In total 47.3% of patients died. Of these 11 deaths (25%) due to thymoma and 5 deaths due to secondary cancers
4	Aiyekomogbon[20] …2017	29	M	Coughs, vomiting, headache, dysphagia to solid meals, SVCS	Malignant thymoma	Debulking surgery, Radiation and Chemo plan	Died from cardiac arrest in intensive care
5.	Mathiselvan[18] ..2019	40	F	Left infraclavicular pain	Type B2 thymoma	Chemo	Relief of tumour related symptoms
6	Salem[16]… 2019	28	F	MG symptoms, tongue atrophy, dysarthria	Benign thymoma	Surgery	Relief from supportive and symptomatic management
7	Peng[12] …2019	3	F	Dyspnoea, Massive pleural effusion, SVCS	Type B2 thymoma	Surgery, Adjuvant Chemo	Alive and well at 6 years follow up, No residual tumour or recurrence detected
8	Baram[10] …2019	Mean (48.5 ±11.6 years)	46 Males 43 Females	Dyspnoea, chest pain, MG symptoms	Types A and AB variants	Surgery, Chemo and Radiation (selected patients)	Variable overall survival, Local recurrence in 4 patients
9	Sousa [4]..2019	49	F	Occasional dyspnea, Fatigue	Type B1 thymoma	Surgery, Radiation, Maintenance pharmacotherapy	No features of recurrence, good response
10	Tayabali [6].. 2020	53	F	Exertional dyspnea, chest pain, weight loss, low appetite, hypotension	Invasive thymoma	Surgery, Chemo, Radiation	Alive on monitoring, 2 month long recovery
11	ES-Sabbahi[17].. 2021	51	F	Dyspnoea, heaviness in the chest	Type AB, Lung spread	Chemo about	Good response, decreased mass size, disappearance of lung nodules
12	Akpor… Index case	61	M	Exertional dyspnea, Chest pain	Type AB (mixed) thymoma	Chemo ± Surgery ± Radiation	Died 18 months later

Keys: MG *myasthenia gravis*, SLE *systemic lupus erythematosus*, Chemo *multiagent chemotherapy*, SVCS *superior vena cava syndrome*

Fatigue, occasional dyspnoea and dyspnoea on exertion, intermittent chest pain, and weight loss have been reported as characterstic symptoms of these mediastinal tumours in general,[4,6,7] with associated presentations of myasthenia gravis (MG)[7] The patient presented in this report was a 61 year old male who had suffered from dyspnoea on exertion, and a right sided chest pain. Until his demise, he was in his 7th decade of life and his symptoms were in keeping with many other patients' presentation in the literature reviewed,[6,7] (see table above). In a series of 89 patients reviewed by Baram et al,[10] the mean age (of 48.5 ± 11.6 years) was basically younger than the age of the index case, but their symptoms were essentially similar and were also associated with the autoimmune disorder myasthenia gravis. Karras et al,[11] (in France) had reported an autoimmune-mediated thymoma-associated nephropathy, further reiterating the quite heterogenous picture sometimes seen in the presentation of thymomas.[9] It is not quite clear or understood, the basis of the autoimmune paraneoplastic syndromes that have been found in association with the thymomas, although they have helped to make the diagnosis relatively easier or straight forward.[2,7] The tumour or even its treatment could likely have produced an effect of immune disturbance on other tissues or organ systems when these autoimmune syndromic presentations are encountered.[9]

Over 37% of the patients studied by Baram et al,[10] were exposed to cigarette smoke at the time of the study, and 6.7% of them were former smokers. Although this has not been established as an aetiologic or risk factor, the patient in our report had also given a history of using cigarettes over 30 years prior to his presentation and confirmation of the tumour in his mediastinum as a thymoma. This might just be a call to further research in the future to determine a likely or possible impact of tobacco on the pathogenesis of thymic tumours.

The diagnostic and treatment challenges posed by these tumours are further betrayed by the finding of a rapidly progressive and invasive thymoma in a three year old girl by workers in Taiwan.[12] In a majority of the cases, the diagnostic approach is to begin with imaging studies like the CT (computerized tomography) scan before progressing to harvest surgical biopsy or resection specimens, and subjecting such to histological examination.[12-14] Just as the case we report, Es-sabbahi et al,[17] also reported a WHO type AB (mixed) thymoma, that was first evaluated by using CT scan, followed by an image guided tumour biopsy taken, and finally confirmed by histopathological examination. Their patient was a 51 year old female, and had received chemotherapy in three (3) cycles, with attendant good response shown by a decrease in the tumour size. Where as this patient was 10 years younger than our patient, and had experienced her symptoms for 5 months before presenting, the index case had experienced over 6 month symptom duration before seeking intervention. In addition to some delay in arriving at a final histologic diagnosis (an earlier report from another centre showed the tumour to be an adenocarcinoma), the patient was also not too compliant with the adjuvant chemotherapy regimen prescribed for him. After over one year and a half of commencing his management and chemotherapy, he passed on without much improvement. A much younger patient, 29 year old male and a 40 year old female respectively from North central Nigeria,[20] and South Africa,[18] were both diagnosed with malignant thymoma. While the younger male patient who suffered from a superior vena cava syndrome and other symptoms for 4 months had died of cardiac arrest during intensive care management, the older female patient had survived with a relief of her tumour related symptoms.[18,20] It may seem that, regardless of the age at diagnosis, female patients tend to have a better outcome or response to treatment, though this is yet to be proven by any conducted research work. This inference in any case appears to be consistent with the reports of few other authors reviewed in this article (Peng et al,[12] Es-sabbahi et al[17],Mathiselvan et al).[18] It is still difficult or controversial to state categorically, if the histological type has a significant impact on survival outcomes and the prognosis of thymomas. By the WHO scheme, Kuo et al,[2] in their observation do not think the histological classification standing on its own has a significant bearing on the prognosis, except in concert with the clinical stage. Harnath et al[7] however concluded that, the tumour histology combined with, the completeness of surgical resection are key determinants of survival outcomes.

CONCLUSION

Despite the present lack of standard guidelines for the management of thymomas, and the fact of their rarity, we advocate that some degree of suspicion should still be entertained when evaluating tumours of the mediastinum and thoracic region in general. Early presentation to allow for early surgical sampling for definitive histological diagnosis, combined with complete tumour resection and adjuvant treatment options are likely to improve the prognosis and survival outcome in patients with thymoma.

CONSENT

Formal informed consent was sought from the relative of the deceased. Although anonymity cannot be guaranteed, he understands that the identity or initials of the patient will not be used in the publication of this article.

CONFLICT OF INTEREST

The authors have no conflicting interests in the publication of this article.

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