Cytogenetic Profile of a Thymoma

A Case Report and Review of the Literature

Imran Mirza, MD, MS; Syed Nadeem Kazimi, MD; Richard Ligi, MS; Jacqueline Burns, PhD; Frank Braza, MD

• Cytogenetic analysis of mixed lymphocyte and epithelial thymoma in a nonmyasthenic female patient revealed deletion of part of the short arm of chromosome 6. To our knowledge, this cytogenetic abnormality in a benign thymoma has not been previously described in the literature, which is reviewed.

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Thymomas are anterior mediastinal tumors that originate from the thymic epithelial cells. These tumors are histologically benign and have been traditionally classified as predominantly lymphocytic, predominantly epithelial, mixed lymphocytic and epithelial, and spindle cell thymoma.[1] Another histogenetic classification scheme proposed by Marino and Muller-Hermelink[2] and elaborated by Quintanilla-Martinez and colleagues[3] is based on the resemblance of the neoplastic cells to various normal thymic epithelial cells. The 4 subtypes of thymoma defined by these authors include medullary, mixed medullary and cortical, predominantly cortical (organoid), and cortical. Of note, the mixed category in the 2 classification schemes refers to entirely different concepts. In the first classification, it refers to an admixture of lymphocytes and epithelial cells, whereas in the latter scheme, it denotes presence of both medullary and cortical-type neoplastic cells. To our knowledge, only 5 thymomas with cytogenetics abnormalities have been previously reported.[4–7] In this report, we present the cytogenetic findings in an additional case of thymoma.

REPORT OF A CASE

A 63-year-old postmenopausal woman was incidentally noted to have a huge mediastinal mass on radiographic examination of the chest during her workup for pneumonia. A computed tomographic scan of the chest showed an anterior mediastinal mass with no evidence of invasion of neighboring structures. Results of serum germ cell tumor markers (α-fetoprotein, β–human chorionic gonadotropin, and cancer antigen 125) were negative. She had no myasthenia-like symptoms, weight loss, night sweats, pruritus, or lymphadenopathy. Her medical history was significant for mitral valve prolapse, hypertension, and hypercholesterolemia. Surgical history included appendectomy and excision of a para-adrenal ganglion excision and multiple basal cell carcinomas. Results of her general physical examination were unremarkable. Cardiopulmonary evaluation showed clear lungs and regular heart rate and rhythm, with occasional premature atrial contractions.

The mediastinal mass was completely resected through a median sternotomy. The tumor approximated the left phrenic vein but did not invade it. Her postoperative course was uneventful, and she was discharged on her fourth postoperative day.

PATHOLOGIC FINDINGS

The tumor was encapsulated and measured 10.0 × 8.0 × 4.3 cm. It showed a lobulated pink-tan cut surface (Fig-

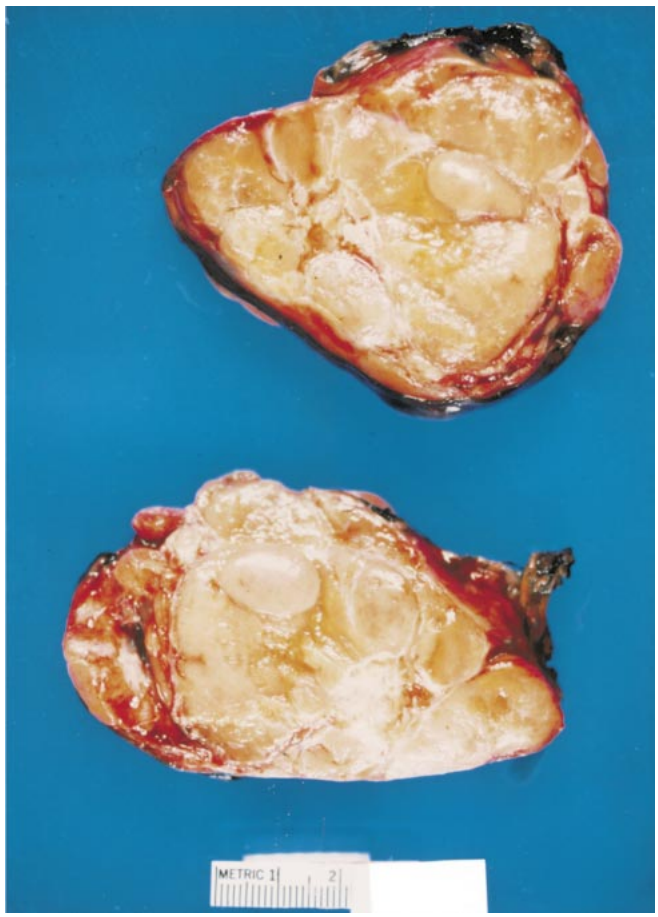

Figure 1. *Well-circumscribed thymoma with lobulated pink-tan cut surface.*

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From the Department of Pathology and Laboratory Medicine, Danbury Hospital, Danbury, Conn.

Reprints: Imran Mirza, MD, MS, Department of Pathology and Laboratory Medicine, Danbury Hospital, 24 Hospital Ave, Danbury, CT 06810 (e-mail: immirza@yahoo.com).

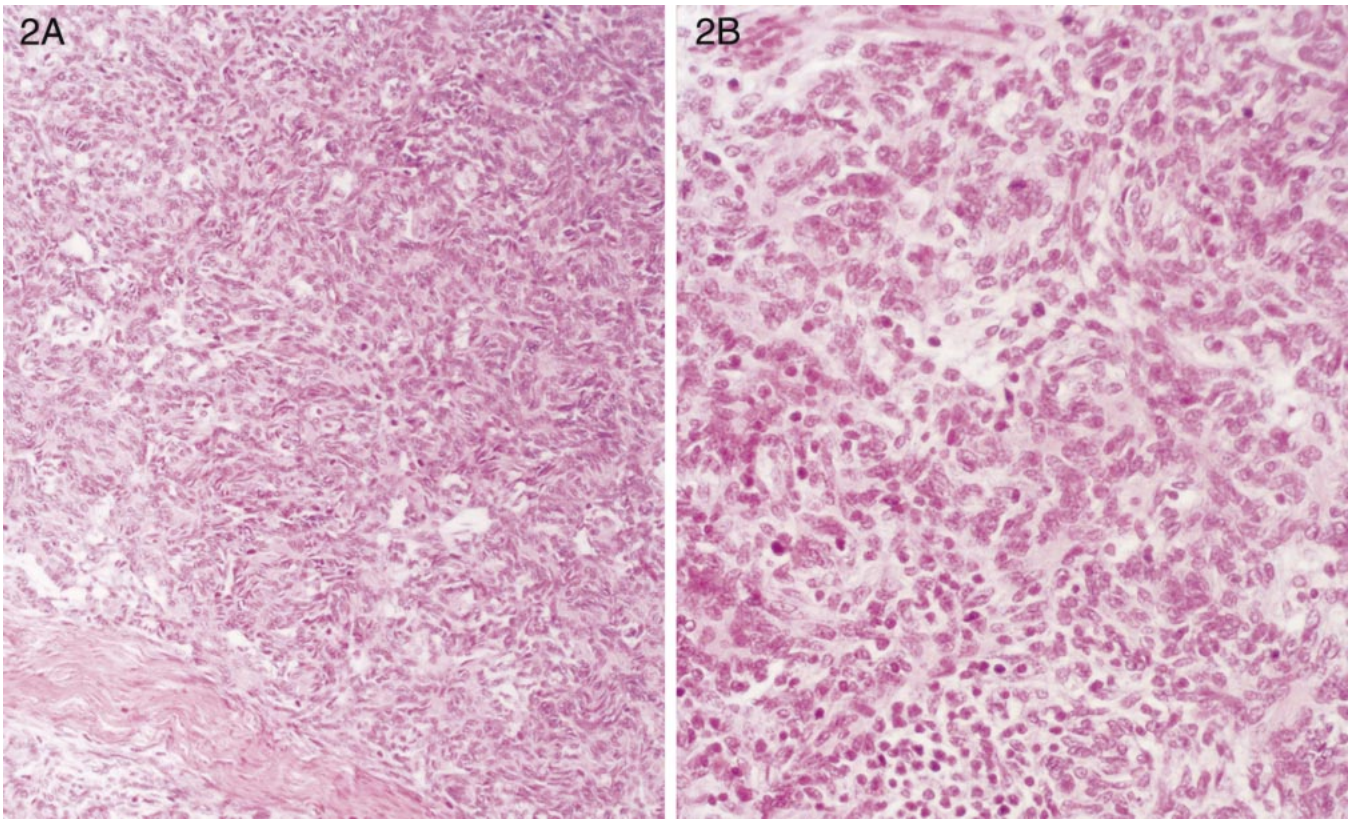

Figure 2. *Thymic epithelial cells with ovoid nuclei lacking atypia and mitotic activity with interspersed small lymphocytes (hematoxylin-eosin, original magnification ×100 [A] and original magnification ×200 [B]).*

Table 1. Reported Chromosomal Abnormalities in Thymomas

Case Number/ Age/Sex	Epithelial Cell Morphologic Findings	Chromosomal Abnormalities	Year/Reference
1/77/M	Cells with large rounded nuclei, distinct nucleoli, and indistinct cytoplasm	44,XY,+X,inv(2)(p25q13),del(6)(q15),−8,−16,−17[8]/46,XY[3]/92,XXYY[2]	1989[4]
2/76/F	Cells with oval or spindle-shaped nucleus and small nucleoli	48-49,XX,+del(X)(q24),+I(5p),+?del(7) q22),der(11)t(1;11)(q23;q25),t(11;?)(p15;?),−18,+r[13]/46,XY[7]	1989[4]
3/71/M	Round to oval cells	46,XY,r(6)	1993[5]
4/70/F	Spindle-shaped cells	46,XX,t(15;22)(p11;q11)[20]	1996[6]
5/61/M	Polygonal, cuboidal, or oval cells with mild atypia	57,X,−Y,+I(1)(q10),+add(4)(q12),+7,+8,+8,+9,+14,+14,+15,+16,der(17)t(9;17) (q13;p13),+20,+22[6]/46,XY[14]	1999[7]
6/63/F	Spindle-shaped cells	46,XX,del(6)(p22p25)[3]	Present case

ure 1). Histologic sections showed a cellular tumor with a prominent lobular pattern. The lobules were separated by thick collagenous septa arising from the capsule. The neoplasm was predominantly composed of spindle-shaped epithelial cells with ovoid nuclei lacking atypia or significant mitotic activity (Figure 2). Perivascular spaces, occasional rosettes, and scattered aggregates of small mature lymphocytes were also seen. There was no evidence of capsular penetration by the tumor. A diagnosis of spindle cell thymoma (medullary thymoma according to the Marino and Muller-Hermelink classification) was rendered.

Cytogenetic Findings

A small piece of fresh tumor tissue was treated according to the procedure previously described for cytogenetic analysis of human solid tumors.[8] The yield of G-banded metaphase cells was poor, with only 3 metaphases, all of which exhibited a female karyotype with a partial deletion of the terminal region of short arm of chromosome 6. The karyotype was interpreted as 46,XX,del(6)(p22p25)[3] (Figure 3). We accepted these results to represent a clonal population of tumor cells according to the recommendation of *ICSN (1995): An International System for Human Cytogenetic Nomenclature,* which defines a clone as having at least 2 cells with the same aberration.[9] These minimum requirements refer to losses in structural aberrations of chromosomes.

COMMENT

In this report, we present an additional case of thymoma with a clonal pattern of deletion of part of the short

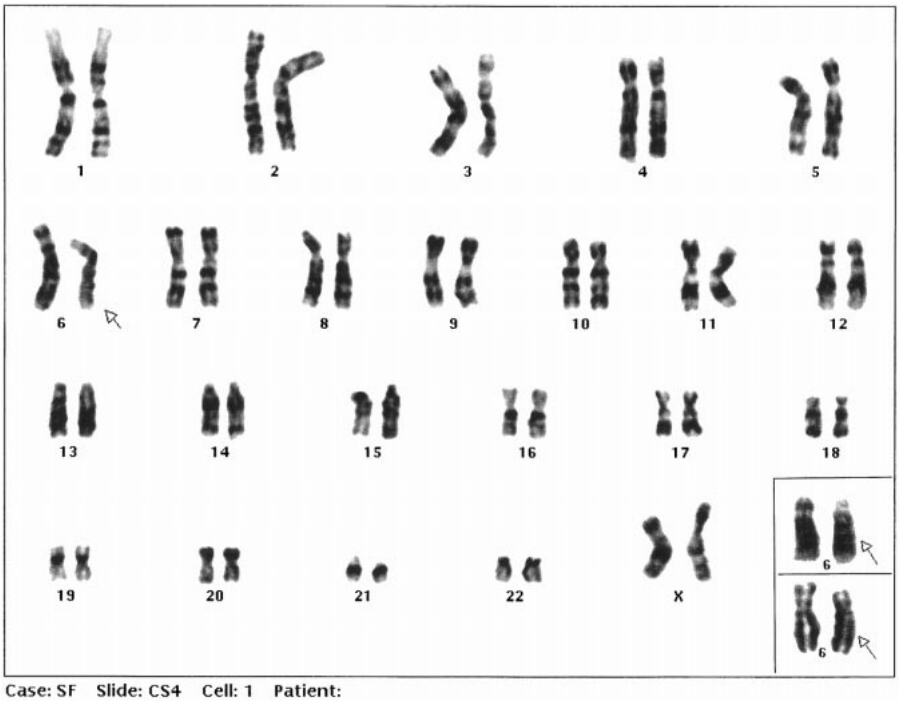

Figure 3. *G-banded karyotype with arrow indicating partial deletion of the terminal region of short arm of chromosome 6. Inset: chromosome 6 in the other 2 cells with same partial deletion.*

arm of chromosome 6. Review of the literature revealed only 5 other case reports of cytogenetic abnormalities in thymomas (Table). There were no associated myasthenic or paraneoplastic symptoms in all these cases. Of these previously reported 5 cases, only 2 had chromosome 6 aberrations (cases 1 and 3). In case 1, deletion of a segment of long arm of chromosome 6 was noted as a part of complex clonal abnormalities.[4] In case 3, a ring chromosome 6 was the only abnormality detected.[5] Deletion of the short arm of chromosome 6 has also been reported in various other hematologic malignant neoplasms, including lymphoid and myeloid lesions.[10–12] The significance of this abnormality in the present case is unknown.

Thymomas may occasionally invade adjacent structures and behave as malignant tumors.[13] Of the 5 previous reports of cytogenetic abnormalities in thymomas, invasion of the adjacent structures was only noted in case 2. However, the reported 8-month follow-up in this patient showed absence of disease symptoms after incomplete resection of the tumor. The histologic features of cases 2, 4, and 6 allow for classifying these 3 tumors as spindle cell thymomas (medullary thymomas). The other 3 cases (1, 3, and 5) could be classified as mixed lymphocytic and epithelial thymomas (possibly mixed or predominantly cortical according to the Marino and Muller-Hermelink classification). The chromosomal abnormalities in these 6 reported cases range from an interstitial deletion to complex chromosomal rearrangements, losses, and gains. The unique t(15;22)(p11;q11) noted in case 4 is not known to occur in other tumors.[14] However, the scarcity of reported cytogenetic abnormalities in benign thymic tumors poses difficulties in determining significance of the observed chromosomal aberrations and in correlating cellular morphologic findings with cytogenetic findings. Cost considerations and technical difficulty of culturing benign solid tumors may have contributed to the paucity of cytogenetic studies in these neoplasms. Another possibility is that a number of these tumors may frequently have normal karyotypes and, therefore, are not reported. With more thymomas being cytogenetically analyzed, one could speculate that recurring cytogenetic abnormalities with possibly consistent molecular rearrangements or loses may be revealed.

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