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Mediastinal germ cell tumour associated with Klinefelter syndrome

A report of case and review of the literature

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Abstract. A 14-year-old boy with Klinefelter syndrome (KS) and a large mediastinal tumour is presented. Human chorionic gonadotropin and oestradiol were markedly increased. An attempt at radical resection was performed. Histological examination revealed a malignant germ cell tumour of mixed histologic pattern composed of choriocarcinoma and components of mature teratoma. Four courses of cisplatin, bleomycin, and etoposide were given. The patient is without any evidence of tumour recurrence 20 months after diagnosis. A review of the literature revealed another 40 cases of primary mediastinal germ cell tumour (PMGCT) associated with KS. Compiled data from larger series demonstrate that at least 8% of male patients with PMGCT have KS, 50 times the expected frequency. In contrast to PMGCT in patients without KS, all tumours were of nonseminomatous histology, and the average age was considerably lower, Tumours in prepubertal boys were associated with precocious puberty.

Key words: Choriocarcinoma – Oestradiol – Human chorionic gonadotropin – Klinefelter syndrome – Primary mediastinal germ cell tumour

Introduction

Primary mediastinal germ cell tumour (PMGCT) is a rare malignancy occurring mostly in young men. In a review of 2399 patients with primary mediastinal tumours, germ cell tumours constituted 10% [8]. PMGCT are most frequently located in the anterior mediastinum where they constitute 15% of all tumours in adulthood and 24% in childhood [35]. In three series of a total of 388 children and adolescents with germ cell tumour only 16 (4%) occurred in the mediastinum [29, 31, 50].

Klinefelter syndrome (KS) is present in about 1 out of 600 males [18] and has been reported associated with PMGCT [3, 5–7, 10, 12–16, 21, 23, 24, 26, 27, 30, 33, 36, 37, 39–41, 43–48]. Some other malignancies have also been reported in association with KS [1, 17, 28, 42]. This paper presents a case of mediastinal malignant germ cell tumour in an adolescent with KS, successfully treated with surgery and intensive chemotherapy. A review of PMGCT associated with KS is presented.

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Abbreviations: AFP = alpha-foetoprotein; HCG = human chorionic gonadotropin; FSH = follicle stimulating hormone; KS = Klinefelter syndrome; LH = luteinizing hormone, PMGCT = primary mediastinal germ cell tumour

Case report

A 14-year-old boy of Asian origin was admitted with a 3-week history of progressive dyspnoea and chest pain. A chest X-ray film showed a large mass in the right hemithorax dislocating the mediastinum and heart to the left. CT-scan demonstrated extensive pleural effusion and a large $8 \times 8 \times 10$ cm tumour occupying almost the entire lower half of the right hemithorax. Acute lateral thoracotomy with the intention of obtaining a histological diagnosis and to remove the tumour, if necessary, had to be interrupted because of excessive bleeding. Arteriography was then performed and showed that the main blood supply came from the two internal thoracic arteries. At the following sternotomy the two arteries were ligated. The tumour was found to invade the pericardium and the right lung. Radical surgical resection was attempted.

Histological examination revealed a very vascular malignant germ cell tumour of mixed histologic pattern. Approximately 66% of the tumour was dominated by a choriocarcinoma component with positive cytoplasmic staining for human chorionic gonadotropin (HCG) and negative for alpha-foetoprotein (AFP) (Figs. 1,2). The remaining 33% of the tumour consisted of mature teratoma. Tumour cells were found in the resection border.

At the initial examination bilateral gynaecomastia, advanced pubic hair development, and small testes were observed. Height 169 cm, weight 49 kg. Ultrasound of the testes showed no focal abnormalities. Karyotyping of cells from bone marrow and peripheral blood all showed 47,XXY.

Chemotherapy was initiated with cisplatin 40 mg/m^2 day 1–5, etoposide 150 mg/m^2 day 1–5, and bleomycin 10 mg day 1–5. All drugs were administered intravenously every 3–4 weeks. A total of four courses was given. Cisplatin was reduced to 25 mg/m^2 during the last course due to impaired renal function.

Serum HCG at presentation was 110.000 IU/l. Serum AFP was normal. During the treatment HCG declined rapidly and remained

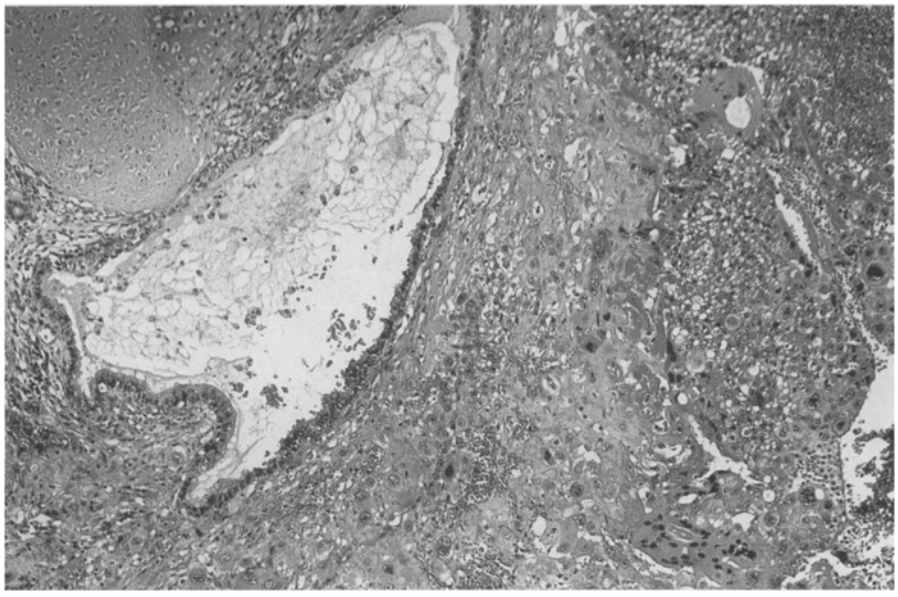

Fig. 1. Teratoma elements forming cartilage and glandular structure *(left part)* and choriocarcinoma *(right part)*. (H & E × 80)

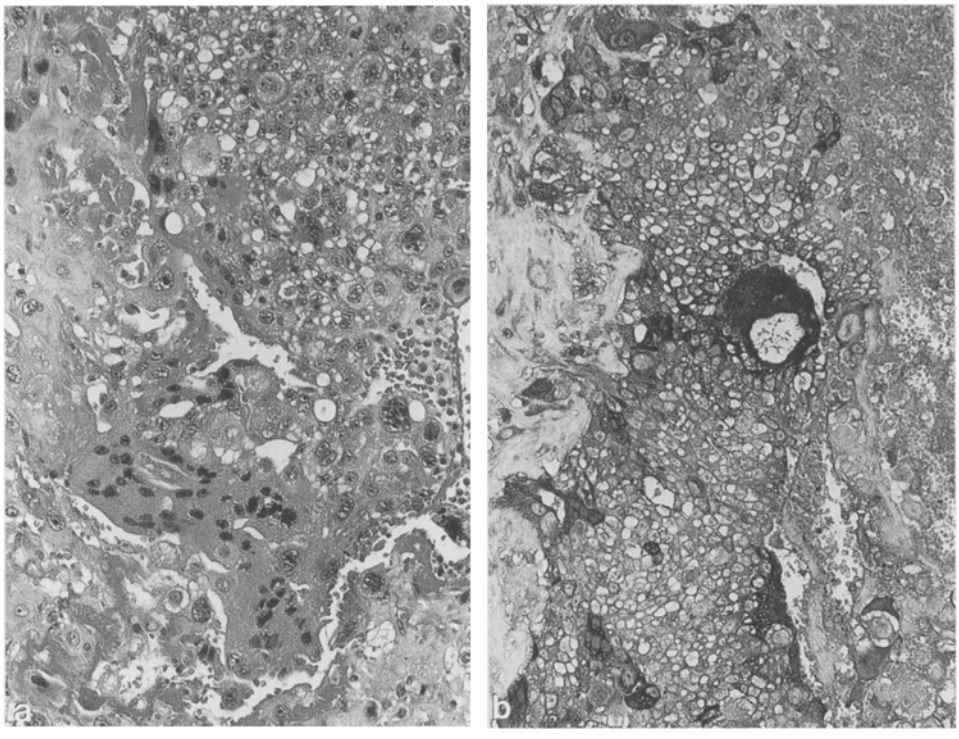

Fig. 2. a Higher magnification of the lower right corner in Fig. 1. Choriocarcinoma with vascular clefts lined with cytotrophoblasts and cyncytiotrophoblasts (giant cells). (H & E × 240). **b.** Choriocarcinoma with positive immunoreactivity for HCG (black reaction), especially in the cyncytiotrophoblasts (HCG × 200)

below the detection limit of 10 IU/l. The serum oestradiol level was increased on admission to 365 pmol/l (reference range in adult men: 48–165 pmol/l) and showed a decline simultaneously to HCG and remained below the detection limit of 40 pmol/l. The testosterone level was low at presentation: 7.1 nmol/l (reference range in adult men: 12–32 nmol/l). The testosterone level increased afterwards and remained in the lower half of the reference range. Luteinizing hormone (LH) at diagnosis could not be determined because of the high HCG concentration. One year later it was 78 IU/l (reference range: 5–20). Follicle stimulating hormone (FSH) at diagnosis and 1 year later was respectively 5.2 and 125 IU/l (reference range: 3–15). The elevated LH and FSH levels are in accordance with the primary hypogonadism. The gynaecomastia disappeared during the treatment.

Table 1. Frequency of KS in larger series of male patients with PMGCT

Authors	No. of PMGCT	No. of KS
Knapp et al. [22]	48	0
Recondo and Libshitz [41]	17	1
Economou et al. [12]	28	1
Dexeus et al. [10]	19	4
Nichols et al. [36]	22	5
Total	134	11 (8%)

Table 2. Summary of all cases identified from the literature of PMGCT associated with KS

First author [reference]	Age	Chromosome analysis	Elevated		Histology
			AFP	HCG	
Recondo [41]	NS	NS	NS	NS	NS
Economou [12]	NS	NS	NS	NS	Nonseminomatous (NS)
Nichols [36]	14	NS	NS	NS	Nonseminomatous (NS)
Nichols [36]	15	NS	NS	NS	Nonseminomatous (NS)
Nichols [36]	15	NS	NS	NS	Nonseminomatous (NS)
Nichols [36]	18	NS	NS	NS	Nonseminomatous (NS)
Nichols [36]	28	NS	NS	NS	Nonseminomatous (NS)
Lachman [24]	19	47,XXY	+	+	Teratoma
Dexeus [10]	31	47,XXY	NS	NS	Teratoma
Kalifa [21][b]	5	47,XXY	−	+	Mature teratoma
Vanfleteren [48]	17	47,XXY	+	+	Mature teratoma
Fujimoto [16]	19	47,XXY	+	+	Mature teratoma
Kalifa [21]	6	47,XXY	−	+	Immature teratoma
Floret [14][c]	8	47,XXY	+	+	Immature teratoma
Pierson [40]	8	47,XXY	NS	NS	Immature teratoma
Penchansky [39]	9	47,XXY	NS	NS	Immature teratoma
Kalifa [21][b]	9	47,XXY	+	+	Immature teratoma
Kalifa [21]	15	47,XXY	NS	NS	Immature teratoma
Landanyi [26]	16	47,XYY	NS	NS	Immature teratoma
McNeil [33]	16	47,XXY	+	−	Embryonal carcinoma
Turner [46]	20	47,XXY	NS	NS	Embryonal carcinoma
Feun [13]	26	NS	NS	NS	Embryonal carcinoma
Dexeus [10]	24	47,XXY	NS	NS	Endodermal sinus tumour
Sogge [44]	26	47,XXY	NS	+	Endodermal sinus tumour
Storm [45]	16	Barr body	−	+	Choriocarcinoma
Curry [6]	20	47,XXY	NS	+	Choriocarcinoma
Sogge [44]	21	47,XXY	NS	NS	Choriocarcinoma
Lee [27]	25	47,XXY	−	+	Choriocarcinoma
Schimke [43]	26	47,XXY	−	+	Choriocarcinoma
Dexeus [10]	18	48,XXYY	NS	NS	Mixed (GER, T)
König [23]	8	47,XXY	+	+	Mixed (GER, T, ES, CH)
Curry [6]	16	47,XXY	+	−	Mixed (T, EC)
Dexeus [10]	16	47,XXY	NS	NS	Mixed (T, EC, ES)
Mann [30]	18	47,XXY	+	+	Mixed (MT, EC)
Nielsen [37]	25	NS	+	−	Mixed (MT, ES)
Valdés-Dapena [47]	12	NS	NS	NS	Mixed (MT, CH)
Present case	14	47,XXY	−	+	Mixed (MT, CH)
Beasley [3]	10	47,XXY	+	+	Mixed (MT, ES, CH)
Danon [7][a]	7	47,XXY	+	+	Mixed (MT, EC, ES, CH)
Turner [46]	23	47,XXY	+	NS	Mixed (EC, ES)
Turner [46]	15	47,XXY	+	+	Mixed (ES, CH)

NS, Not specified; GER, germinoma; T, teratoma; IT, immature teratoma; MT, mature teratoma; EC, Embryonal carcinoma; ES, endodermal sinus tumour; CH, choriocarcinoma; Mixed, malignant germ cell tumour of mixed histologic pattern

[a] Only later recognized as Klinefelter Syndrome [5, 14]

[b] Previously presented by Chaussain et al. [5]

[c] Previously presented by Floret et al. [15]

The patient is without any evidence of tumour recurrence 20 months after the initial presentation and 16 months after cessation of therapy.

Discussion

Two recent reviews [10, 19] identified about 30 extragonadal germ cell tumours associated with KS. Most of them appeared in the mediastinum (73% and 91%, respectively). There have been only a few reports of testicular tumours in patients with KS [4].

In lack of cohort studies, the incidence of PMGCT among patients with KS must be estimated from larger series of PMGCT. The presence of KS may be overlooked because HCG-producing tumours per se may induce gynaecomastia [49] but should be suggested by the

presence of small testes. However, KS may easily be overlooked in prepubertal boys, and infertility in boys who have survived a germ cell tumour may be considered as therapy related.

The reported frequency of KS in male patients with PMGCT varies from 0% to 22% (Table 1). The true frequency is probably closer to 20% because it was higher in the only two studies with prospective cytogenenetic studies of all patients [10, 36]. When the data from the Table are compiled, the 11 cases with KS constitute 8% of the 134 patients, which is about 50 times the expected number when compared to the prevalence of KS in the general population of 1/600 [18].

Available data of all patients identified in the literature with KS and PMGCT are presented in Table 2. The mean age was 17 years (range 5–31) compared to 29 years (range 2–67) in patients without KS [22]. In all cases where the tumour occurred in children below the age of 12, it was associated with precocious puberty [3, 7, 14, 21, 23, 39, 40]. PMGCT was almost exclusively associated with the classic form of KS (with the karyotype 47,XXY) which was identified in 29 of the 30 patients with a full chromosomal analysis. If the patients reported by Nichols et al. [36] are included, the 47,XXY karyotype constituted 32 out of 33 cases. The remaining patient showed the karyotype 48,XXYY. No cases of XY/XXY mosaicism were found. In the Danish Cytogenetic Register the karyotype 47,XXY constituted 87% of the 637 patients with KS [38].

In the review presented in Table 2 the histology is classified according to Dehner [9]. The Table demonstrates that the entire histological spectrum of mediastinal germ cell tumours has been reported in association with KS except the pure germinoma. In patients without KS, germinoma is the most common histological subtype of PMGCT [35]. One case of metastatic mediastinal germinoma associated with KS has been reported [11]. As a remarkable contrast, cerebral germ cell tumour associated with KS have all been of the germinoma type [2].

Choriocarcinoma is reported to occur at a higher relative frequency in patients with KS [10]. The present review of 41 patients revealed 11 with a chorocarcinoma component. When data from larger series of PMGCT [12, 20, 22, 25] are summarized, choriocarcinoma (pure or mixed) accounts for 25 of the 96 cases of nonseminomatous PMGCT. Accordingly, when only the nonseminomatous tumours are considered the relative frequency of choriocarcinoma is comparable in patients with and without KS. However, major concern is connected with mediastinal choriocarcinoma because of the increased risk of haemorrhage during surgical procedure [32] and the risk of pericardial involvement, as observed in our patient.

The genesis of extragonadal germ cell tumours is supposed to be related to incomplete migration of the primordial germ cell from the endoderm of the yolk sac to the gonads, resulting in later malignant transformation to midline germ cell tumours along the urogenital ridge [41]. The more frequent neoplastic transformation of germ cells in KS might be a result of the disarrangement of the hormonal milieu with persistent elevation of FSH and LH. Indirect evidence of increased susceptibility to oncogenic stimuli derives from a patient with XY/XXY mosaic, where the XXY fibroblasts transformed more frequently when exposed to simian papovavirus [34]. However, these theories cannot explain why the increased risk of germ cell tumours observed with KS is apparently almost exclusively related to nonseminomatous neoplasias of mediastinal location.

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