Virchows Arch (1998) 433:571–574

CASE REPORT

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Intracranial germ cell tumour (embryonal carcinoma with teratoma) with complex karyotype including isochromosome 12p

Received: 24 February 1998 / Accepted: 15 July 1998

Abstract We report the chromosomal characteristics of a malignant teratoma with embryonal carcinoma component located in the pineal region of a 15-year-old boy. Chromosome analysis showed a near-triploid complex karyotype (62 chromosomes), including two copies of an isochromosome 12p, confirmed by fluorescence in situ hybridization analysis. The present findings indicate that isochromosome 12p formation is probably associated with the development of malignant germ cell tumours.

Key words Isochromosome 12p · Brain tumour · Germ cell tumour · Teratoma

Introduction

The incidence of intracranial germ cell tumours (GCTs) varies considerably according to the geographical area, accounting for only 0.3–3% of primary central nervous system neoplasms in Western countries, as opposed to 4–12% in Japan. They are most frequently seen in the young and there is a definite male predominance, with a male-to-female ratio of 2.2:1. At least 80% of these tumours typically arise at midline sites involving the pineal and suprasellar regions, including the hypothalamus and III ventricle [13]. GCTs arising intracranially are histologically identical to those occurring in the gonads and at other extragonadal sites [9].

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Cytogenetic investigations on intracranial GCTs have occasionally been reported, but no clear cytogenetic profile has yet emerged [1–5, 8, 10, 14–18]. There have been reports of an isochromosome of the short arm of chromosome 12 [i(12p)] in two tumours of the pineal region [10, 15], but i(12p) has been seen only as a common chromosome abnormality of GCTs of gonadal and extragonadal sites [12].

We report a case of embryonal carcinoma admixed with malignant teratoma with two copies of i(12p), arising in the pineal region.

Case report

A 15-year-old boy presented with a very short history of headache and vomiting. Computed tomography scan (CT) and magnetic resonance image (MRI) demonstrated a 2-cm mass in the pineal region causing hydrocephalus. Blood concentrations of β-HCG and α-fetoprotein (AFP) were normal.

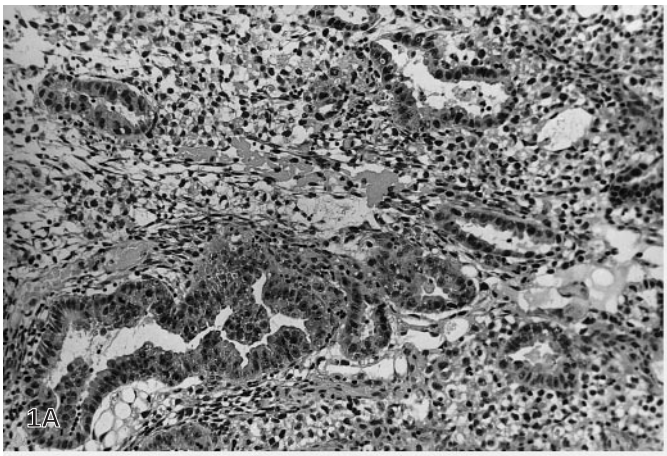
Incomplete resection of a multilobular and incapsulated tumour was performed, because it had invaded the brain stem. Part of the resected tumour was processed for histological examination and part was investigated cytogenetically. Microscopic examination showed that the lesion's predominant component was made up of large cells growing in solid sheets and poorly formed glands. This component occupied 50% of the tumour area. The large cells showed abundant eosinophilic cytoplasm and pleomorphic nuclei with prominent nucleoli. The remaining part of the tumour was made up of nests of malignant cartilage and of squamous cells, intermingled with spindle elements. Numerous mitoses (14/10HPF) and large foci of necrosis were visible (Fig. 1A, B). For immunohistochemistry detection by ABC was used together with the antibodies listed in Table 1. The large cells and the glandular structures and squamous areas showed intense and diffuse cytoplasmic labelling for cytokeratin (Fig. 2A). Several spindle cells and scattered large elements were

Table 1 Source and dilution of antibodies used (*M* monoclonal, *P* polyclonal)

Antibody	Source	M/P	Clone	Dilution
Cytokeratin	Dako	M	MNF116	1 :100
Alpha fetoprotein	Dako	P	1:500	
β–HCG	Dako	P		1:5000
PLAP	Dako	P		1:300

Table 2 Cytogenetic studies of intracranial germ cell tumours with a 12p-chromosome abnormality

Case No	Age(years)/ Sex	Site of primary tumour/ histological type	Abnormal karyotype	Reference
1.	11.5/M	Pineal region/germinoma	75–84,XXYY,-1,-3,add(3)(p21), –4,-4,-7,+8,-9,add(9)(p13),-10, –11,-11,-12,add(12)(p11),-13,-13, –16,i(17q),-18,-19,-20,-20,-22,hsr(?,+5mar)	[1]
2.	16/M	Pineal region/mixed malignant non-seminomatous	64,XY,+X,del(1)(q12),+i(1)(q10),+del(2)(q13q24), +3,+7,+7,+8,+8,+12,+i(12)(p10),+i(12)(p10), +14,+der(17)t(Y;17)(q11;p11),+20,+del(20)(q12), +21,+21,add(22)(p13),+mar	[5]
3.	?/M	Pineal region/mixed tumour	51–229<4n>,XXYY,+X,i(1)(q10),+der(1;5)(q10;p10, –4,-5,i(8)(q10)x2,-9,+10,-11,+12,-13,-14,-16,-17, –18,-19,+21,+21,+add(22)(q13)x2[12]/46,XY[3]	[2]
4.	?/M	Pineal region/germinoma	75–84<3n>,XXY,+Y,+2,add(3)(p21),-4,+5,+6,+8,+8, add(9)(p13),-11,add(12)(p11),-13,+14,+15,i(17)(q10), +18,-20,+21,+hsr,+5mar[14]	[2]
5.	27/M	Pineal region/immature teratoma	79–83,XY,+X,+?i(X)(p10),+i(2)(q10), add(12)(q24),i(12)(p10), der(16)t(1;16)(q21;q24),?i(17)(q10),+5mar	[4]
6.	15/M	Pineal region/mixed tumour	62,X,-Y,+X, der(2)t(2;5)(p12;q15)x2,+3,+6, +7,+8,+8,der(11)t(1;11)(q21;q24),+12, +i(12)(p10)x2,+13,+14,+15,+17,+19,+20,+21,+22	Present case



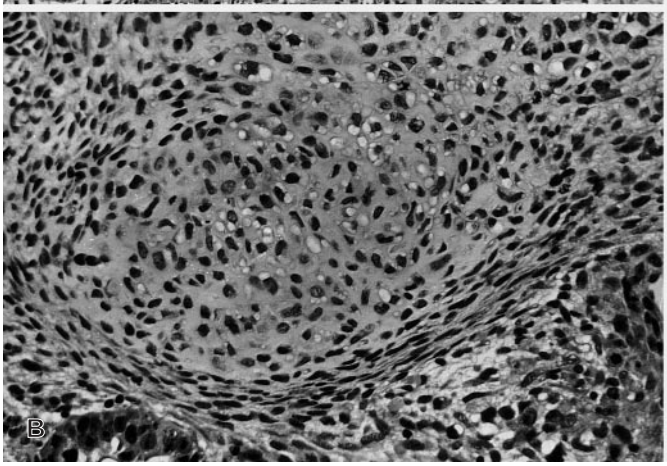
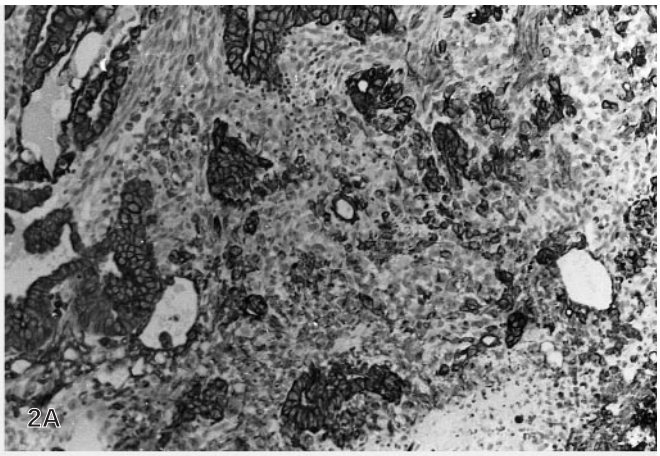


Fig. 1 **A** Poorly formed glands intermingled with cells with clear cytoplasm. HE ×115 **B** Spindle cells and glandular structures surround malignant cartilage. HE ×175



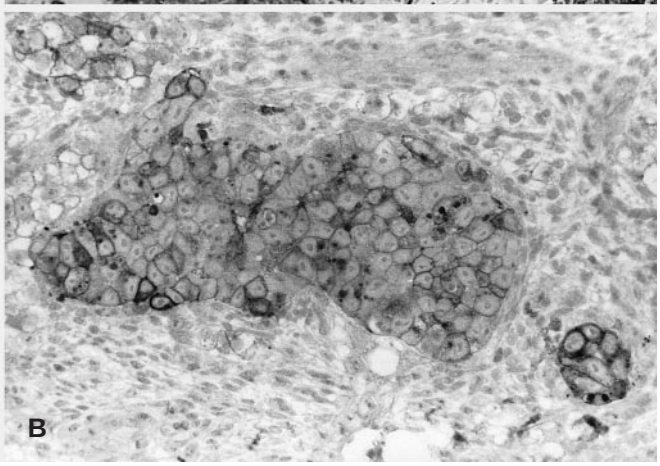


Fig. 2 **A** Glandular structures, spindle cells and large elements positive with anti-cytokeratin antibody. ABC peroxidase, ×115 **B** A solid epithelial area containing cells immunoreactive with anti-PLAP antibody. ABC peroxidase, ×230

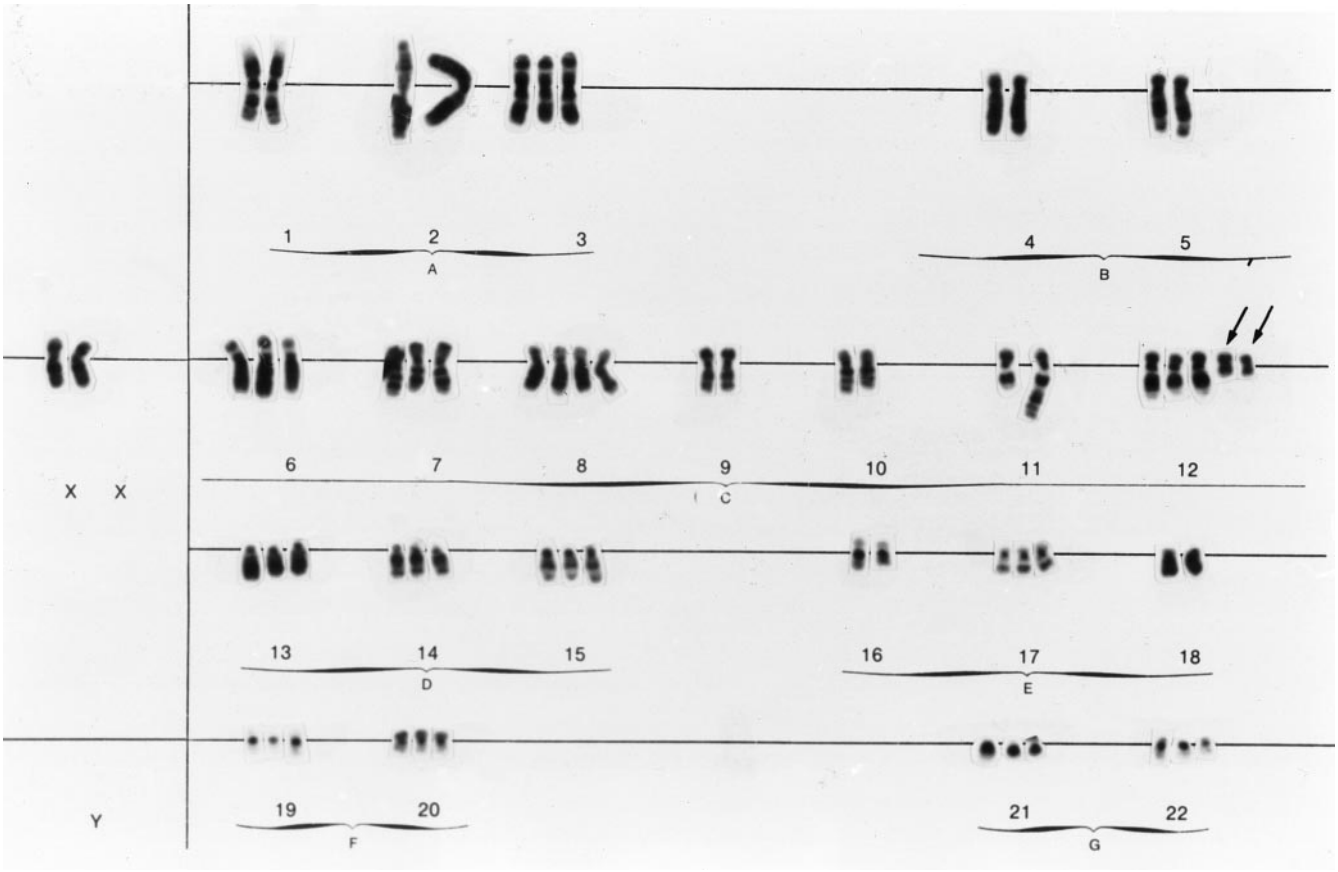


Fig. 3 G-banded karyotype showing the presence of two copies of i(12p)

positive for AFP and for PLAP antisera (Fig. 2B). β-HCG antiserum stained rare large cells. The diagnosis was that of malignant teratoma with an embryonal carcinoma component.

The patient was treated with five cycles of chemotherapy followed by radiotherapy, and is in good health after 6 months.

Cytogenetic and molecular cytogenetics

In all 20 G-banded metaphases obtained after short-term culture (4 days) of a specimen of the tumour that had been collagenase disaggregated overnight, a near-triploid complex karyotype was present:

62,X,-Y,+X, der(2)t(2;5)(p12;q15)x2,+3,+6,+7,+8,+8, der(11)t(1;11)(q21;q24),+12,
+i(12)(p10)x2,+13,+14,+15,+17,+19,+20,+21,+22
(Fig. 3).

Fluorescence in situ hybridization (FISH) was performed using a cosmid 50F4, which contains exon 2 and other more 5' sequences of the ETV-6 gene localized in 12p13.

Labelling hybridization and detection were performed according to standard methods, as previously described

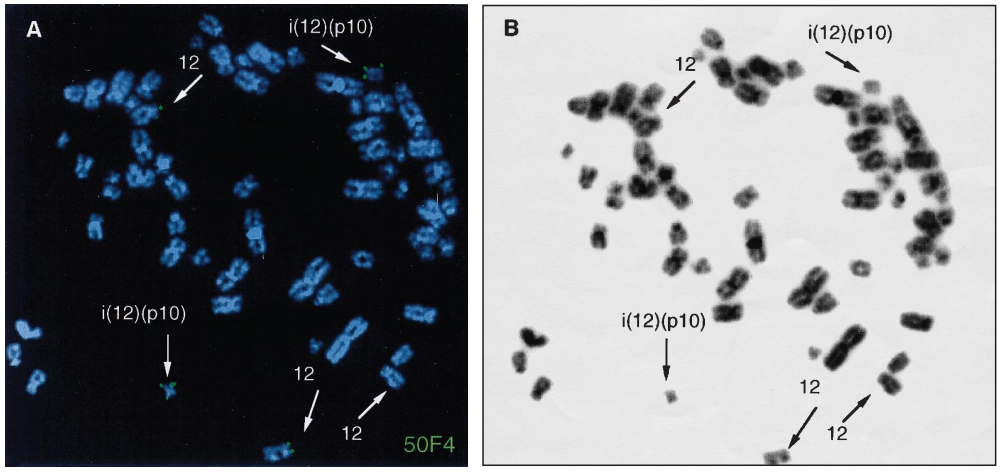


Fig. 4 **A** Metaphase cell showing the presence of two copies of i(12p) and three normal chromosomes 12 (*arrows*) using a cosmid probe 50F4 specific for 12p13.3 (*green*). **B** G-banding karyotype from the same metaphase, counterstained with DAPI

[6]. Twenty-five metaphase spreads were examined, which showed labelling of the short arm of three copies of chromosomes 12 and of both arms of two copies of the small metacentric marker. This confirmed the markers as i(12)(p10) (Fig. 4).

Discussion

This tumour from the pineal region in a male youth was a poorly differentiated embryonal carcinoma, as evidenced by glandular structures formed by cuboidal cells with large nuclei and prominent nucleoli. It contained a malignant teratoma component made up of spindle cells, squamous elements and malignant cartilage [11]. Some of the spindle and large cells were positive with AFP and PLAP antisera. β-HCG antiserum revealed only occasional positive cells. Abundant mitotic activity and necrosis were present.

Of the 17 reported cases of GCTs occurring intracranially in which cytogenetic studies were performed, 12 showed numerical or complex structural chromosomal abnormalities. An apparently normal karyotype was found in 5 [1–5, 8, 10, 14–18]. Table 2 summarizes only those GCTs with a 12p chromosome abnormality. An i(12p) was found in the present case, which thus has to be added to the only two previously reported pineal GCTs showing the same chromosome alteration.

An i(12)(p10) chromosome rearrangement occurring as one or more extra chromosomes has been identified in a variety of testicular GCTs (both seminomatous and non-seminomatous), and also in some GCTs from the ovary and from extragonadal sites occurring around or after onset of sexual maturation. It seems that this particular chromosome change is observed in GCTs wherever they are localized and may play an important part in the pathogenesis of GCTs, regardless of the histological type and site of the tumour [7]. It is not known how large the proportion of GCTs with i(12p) is among intracranial GCTs.

Acknowledgements This text presents research results of the Belgian Programme on Interuniversity Poles of Attraction initiated by the Belgian State, Prime Minister's Office, Science Policy Programming. Scientific responsibility rests with its authors. The authors want to thank Lut Mekers, Belinda Carleer and Betty Emanuel for technical assistance.

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