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CASE REPORTS

Small cell lung carcinoma in a patient with Sotos syndrome: are genes at 3p21 involved in both conditions?

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Abstract

A 22 year old female with Sotos syndrome and a small cell lung carcinoma is described. This case is of interest not only because of the somatic growth pattern, atypical of Sotos syndrome, but also because of the association with a rare tumour. Of significance is the possible role of mutations at 3p21 in the aetiology of Sotos syndrome and tumour development.

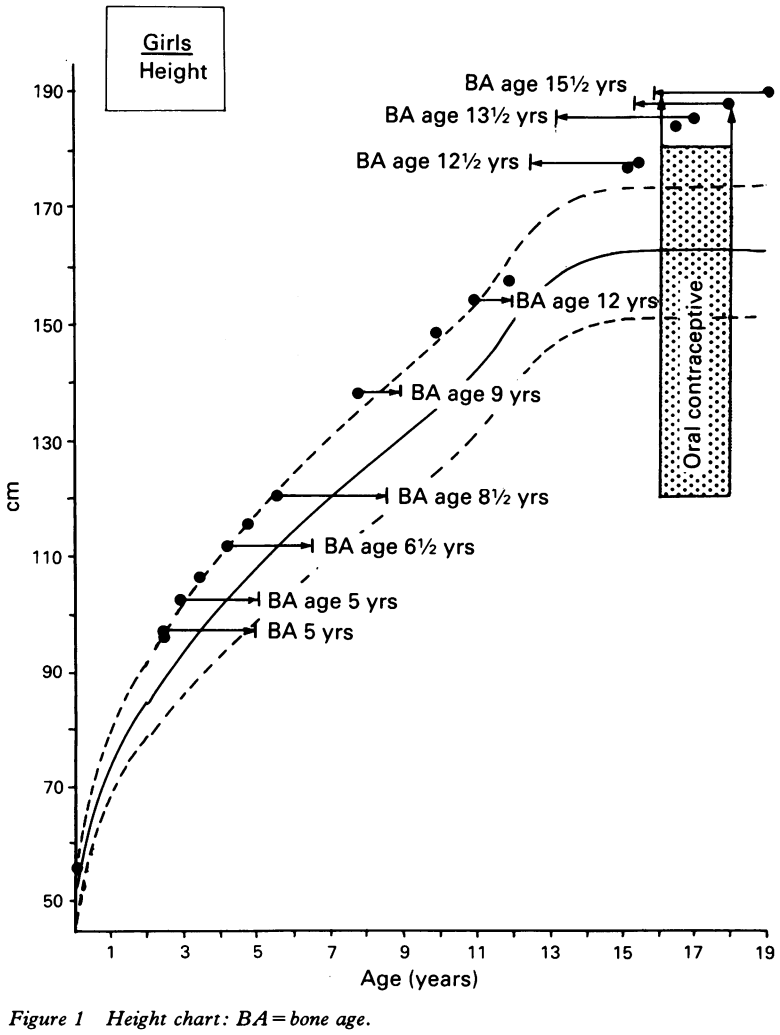

Figure 1 Height chart: BA = bone age.

There are several published reports of tumour formation in overgrowth syndromes.[1-4] Here we describe a patient with Sotos syndrome who died of secondary hepatic tumour deposits at the age of 22 years and where subsequent histological and radiological review indicated that the primary tumour was a small cell lung carcinoma (sclc).

The association of Sotos syndrome and sclc could be significant as loss of heterozygosity of markers at chromosome 3p21 has been identified in small cell lung carcinoma[5] and an apparently balanced de novo translocation with one of the breakpoints at the same locus, 3p21, has been reported in a child with Sotos syndrome.[6] While the involvement of the same chromosome region in these two cases could be coincidental, it could also indicate the localisation of a gene or genes for Sotos syndrome.

Case report

The patient was delivered by forceps at term plus 10 days. Birth weight and length of 4320 g and 56 cm were above the 97th centile and subsequent accelerated growth resulted in gigantic adult proportions (figs 1 and 2).

Early developmental delay and incoordination were documented in the medical records and unsupported walking was not achieved until 22 months. Formal developmental assessments in childhood were in the range of borderline mental handicap but attainment of good social skills and maturity allowed considerable compensation. The patient was in full time employment and independent (fig 3).

Total dental clearance for caries was performed at the age of 16 years; early eruption had not been a feature. Bone age was significantly advanced between the ages of 2½ years and 11 years but subsequently showed marked delay from the age of 15½ years (fig 1). Development of secondary sexual characteristics did not occur until the late teenage years. Menarche had not occurred by the age of 16 years. A combined oestrogen and progestogen oral contraceptive (Marvelon) was prescribed until the age of 18 years in an attempt to bring about fusion of the epiphyses. Spontaneous menarche still had not occurred at 21 years of age when hormone therapy was reintroduced. Withdrawal of oral contraception at the age of

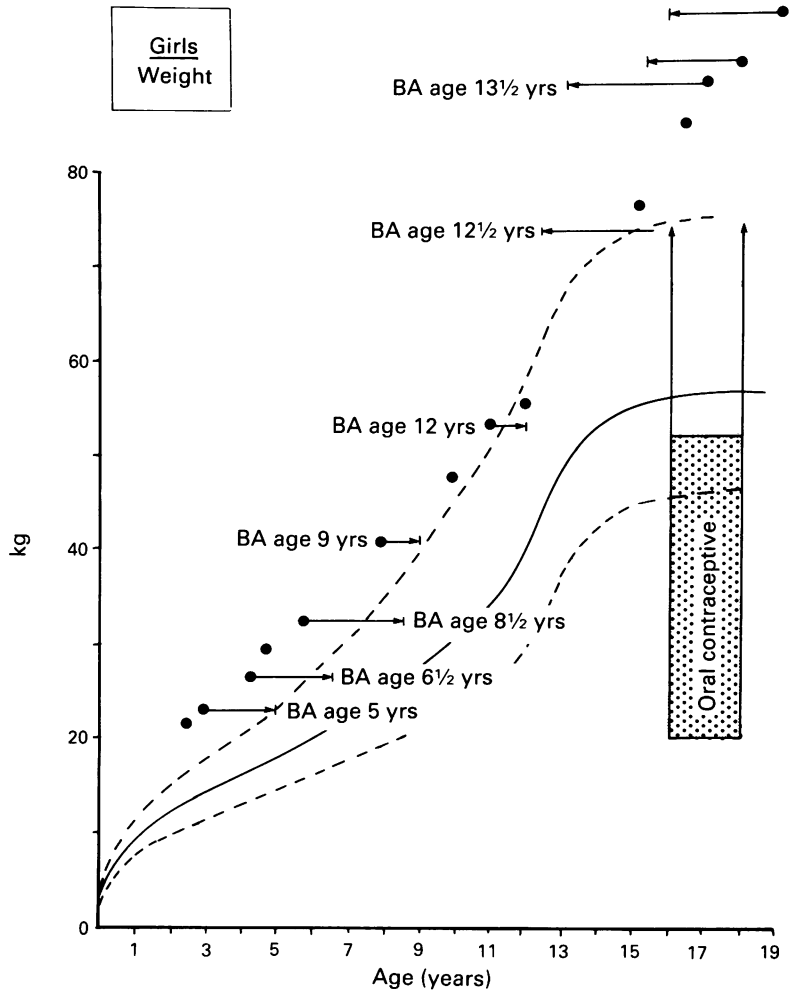

Figure 2 Weight chart: BA = bone age.

Figure 3 Proband aged 22 years.

22½ years was followed by three menstrual flows which then ceased up until the time of the patient's death, four months later.

A month before her death she was admitted with a 5 month history of weight loss (15·8 kg), a non-productive cough, lethargy, and exertional dyspnoea. Immediately preceding her admission she developed oedema of her calves and abdominal fullness. She did not smoke or drink alcohol.

On examination she was anicteric and the only abnormal findings were a systolic murmur, non-pitting oedema of the mid-calves, and an 8 cm tender smooth liver edge with mild ascites. Liver function tests, performed three months earlier, showed mild hepatic dysfunction but these later deteriorated. Hepatitis B surface antigen was negative and alphafetoprotein (11 kU/l, normal < 10 kU/l), thyroid function tests, and the INR were normal (table 1).

Ultrasound and CT scans of the abdomen showed marked hepatomegaly, with a few small foci of reduced attenuation. The intrahepatic portion of the vena cava appeared to be compressed from the left side but no obvious hepatic mass was identified. There was diffuse nodular enlargement of the adrenal glands, (possibly owing to an abnormality in the pituatry adrenal axis) and an unusually low density mass (maximum diameter 2 cm) in the left para-aortic region. Histological examination of a needle liver biopsy showed hepatic tissue widely infiltrated with undifferentiated small cell carcinoma arranged in small islands, the individual cells having nuclei with a fine chromatin pattern and scanty cytoplasm. On review, the provisional diagnosis of hepatoblastoma was thought to be unlikely, and the appearance was more suggestive of a metastatic carcinoma of unknown origin.

Necropsy review of the chest radiograph showed a hyperdense ovoid lesion, measuring approximately 5 × 6 cm. No lateral film was available, but a CT scan showed a lesion within the lung in the lower left field (fig 4).

A full necropsy was not performed but the ovaries and part of the liver were obtained. Both ovaries measured approximately 7 × 5 × 3 cm and had a nodular white homogeneous appearance. Macroscopically both ovaries and the liver were widely infiltrated with tumour. Sheets of small cells, showing either a solid trabecular or acinar arrangement were present. A Grimelius silver impregnation technique showed that a significant proportion of these cells contained argyrophilic cytoplasmic granules and immunocytochemistry showed focal positivity for neurone specific enolase and HMFG2. Further histology was limited by post mortem autolysis. These findings were consistent with a poorly differentiated neuroendocrine cell carcinoma of the small (oat) cell type. In view of the pulmonary tumour identified radiologically, a primary lung tumour was favoured, although similar tumours arising elsewhere could not be completely excluded. Small cell carcinoma of the

Table 1 Endocrine and hepatic investigations.

	30.3.89*	28.5.89*	Range/units
Alkaline phosphatase	96	257	30-95 IU/l
Bilirubin	24	188	3-20 μmol/l
Aspartate transaminase	67	285	12-24 IU/l
γ glutamyl transferase	42	—	3-35 IU/l
Alphafetoprotein	—	11	< 10 kU/l
Luteinising hormone	3·0	—	2-13 IU/l
Follicle secreting hormone	6·1	—	3-12 IU/l
Prolactin	217	—	50-350 mIU/l
Oestradiol	459	—	110-752 pmol/l
Androstenedione	9·5	—	3-10·7 nmol/l
IGF	0·48	—	0·4-2·0 U/ml

* Patient died 6 June 1989.

ovary was thought unlikely since this tumour is rarely bilateral and there was no hypercalcaemia. The possibility of a malignant peripheral neuroectodermal tumour (Askin tumour)[7] was also considered, but the absence of rosettes, along with negative immunostaining for protein S-100, neurofilmament, and glial fibrillary acidic protein make this diagnosis unlikely.

Chromosome analysis, including fragile X, was normal. Biochemical data are summarised in table 1.

Discussion

There are now many published cases of tumour formation in overgrowth syndromes, Beckwith-Wiedemann syndrome being the most frequently reported example.[8] Even increased birth weight alone has been linked to later tumour formation, in particular to leukaemias in children under the age of 2 years.[9] A review by Wit *et al*[2] quotes a 7% frequency for malignant disease in Sotos syndrome. However, of the 10 tumours documented four were non-malignant[10-16] (table 2). In addition, in the series reported by Wit *et al*[2] one case, with colonic polyps, was later diagnosed as Ruvalcaba-Myhre-Smith syndrome, and the neurofibroma reported by Sotos *et al*[17] was in a sib of the index case. Cohen,[8] in a separate review, gives a 3·9% risk of tumour formation, but even this figure is likely to be an overestimate because of biased reporting of concurrence of two rare phenomena.

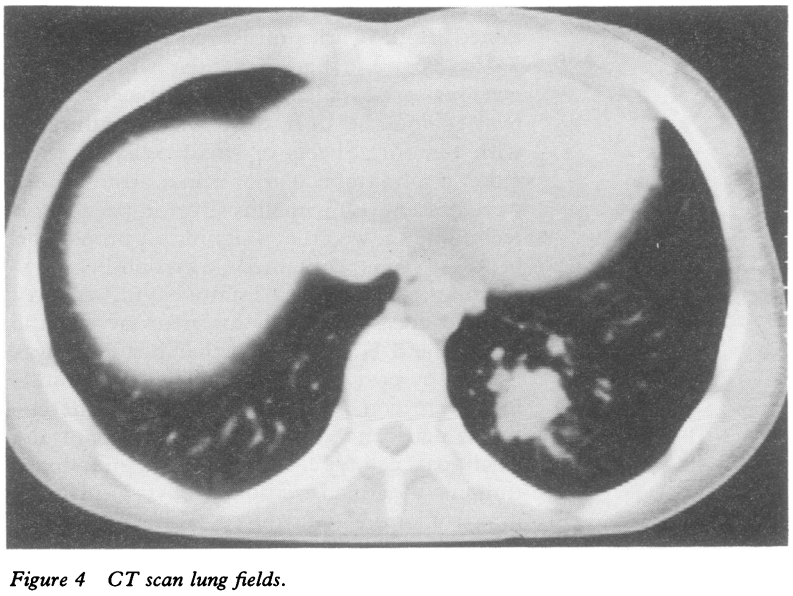

Figure 4 CT scan lung fields.

A recent questionnaire sent to 94 geneticists world wide suggested a tumour incidence of 1·8% in Sotos syndrome (J Hersch, personal communication). This frequency is thought also to be an overestimation as a significant number of cases of Sotos syndrome without tumours may not have been reported. In our own series of 40 'classical' cases of Sotos syndrome (mean age 10·8 years),[18] only one malignant tumour has been identified (the subject of this report), bringing the total number to six in over 250 cases.

This patient is interesting not only because she developed a tumour type previously unreported in Sotos syndrome but she also exhibited an unusual pattern of pubertal development and growth. An atypical pubertal history in females with Sotos syndrome is not uncommon and several cases with early menarche have been reported.[12 18] Consistent with early puberty in adolescent females with Sotos syndrome is significant advancement of the bone age and early fusion of the epiphyses resulting in a final height below the 97th centile. In the authors' own experience, three out of four adult females with Sotos syndrome had final heights between the 50th and 97th centiles.[18] One can speculate whether the atypical growth pattern in this patient predisposed her to tumour development. However, it should be noted that the three other cases of Sotos syndrome reported with post-pubertal tumours did not exhibit a similarly delayed puberty or growth pattern (table 2).

Development of a sclc in the patient is of particular interest as the locus that has been implicated in the development of this tumour, 3p21,[5] is the same as one of the breakpoints in a patient with Sotos syndrome and an apparently balanced de novo translocation reported by Schrander-Stumpel *et al*.[6] Although there are a number of other reports of chromosomal rearrangements in subjects with a 'Sotos-like' phenotype,[19 20] the patient described by Schrander-Stumpel *et al*[6] has the 'classical' Sotos phenotype and therefore the two breakpoints in this case, 6p21 and 3p21 in particular, should be seriously considered as possible localisations for the Sotos gene.

Loss of heterozygosity for markers between 3p21–25 in sclc has been reported by several workers,[5 21] the postulated pathogenetic mechanism being the loss at this locus of a protective or suppressor gene (anti-oncogene) in the tumour, which is present as a single copy in the normal somatic tissue. It is hypothesised that the germline mutation, resulting in the presence of only a single 'normal' somatic copy of the gene, could be responsible for the Sotos phenotype. It may be that the loss of this 'protective' gene is not specific to sclc but has a more generalised effect in the development of several different tumours,[5 22] which might explain the different tumours seen in patients with Sotos syndrome. One possible explanation is that a mutation in the region of 3p21

Table 2 Reported tumours in Sotos syndrome.

Reference	Tumour type	Sex	Birth weight (g)	Age*	Height†	Puberty
		Malignant tumours				
10	Neuroblastoma	F	3890	15m	+	
11	Wilms	F	4000	5y	+	
	Wilms	M	4300	4y	+	
12	Vaginal carcinoma	F	4810	20y	− (7y)	Early
13	Hepatocellular carcinoma	M	3760	14y	+	Normal
Present case	Small cell lung carcinoma	F	4320	22y	+	Delayed
		Non-malignant tumours				
14‡	'Mixed parotid tumour'	F	2270	13y	− (5y)	Normal
15	Cavernous haemangioma	F	2470§	1m	+	
16	'Large hairy naevus'	F	3850	1y	+	Normal
	Osteochondroma	M	2130‖	7y	+	Normal

* Age when tumour diagnosed.
† + = height > 97th centile when tumour diagnosed; − = height < 97th centile when tumour diagnosed (age when height fell below 97th centile).
‡ Diagnosis of Sotos syndrome questionable.
§ At 37 weeks' gestation.
‖ At 31 weeks' gestation.

could remove the suppression from the oncogene v-erb a, which has in fact been localised to this region.

Further molecular investigation of the present case is obviously important in order to identify whether heterozygosity for any markers in the blood has been lost in the tumour tissue.[23 24] To date, this investigation has been hampered by degradation of tumour DNA, most of the DNA extracted being smaller than 2 kb, which is only suitable for PCR amplification. In the long term, cloning and sequencing the DNA across the region of the 3p21 translocation and screening a population of patients with Sotos syndrome for mutations in this region would provide a more definitive answer. Unfortunately, efforts to establish a cell line in the above patient were unsuccessful.

Conclusion

The development of tumours in Sotos syndrome appears to be a rare event. However, the occasional association may be important in the understanding of the aetiology of Sotos syndrome. The possibility of alleles at 3p21 being involved in the causation of Sotos syndrome, as well as having a role in the development of tumours, identifies an exciting area for future research. In addition, this case provides information on an unusual pattern of growth and sexual development in Sotos syndrome. It will be important to note if any subsequent cases that develop tumours have a similar growth pattern.

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