Simultaneous adrenocortical carcinoma and ganglioneuroblastoma in a child with Turner syndrome and germline p53 mutation

E K Pivnick, W L Furman, G V N Velagaleti, J J Jenkins, N A Chase, R C Ribeiro

Abstract

The predisposition to malignancy that is dominantly inherited in Li-Fraumeni syndrome is associated with germline mutations of the tumour suppressor gene p53. Although second malignant neoplasms have been described in children with p53 mutations, the synchronous occurrence of two embryologically different tumours in these children has not been reported. A 20 month old girl with failure to thrive and congenital heart defects was found to have unilateral adrenal masses which, at surgical removal, proved to be an adrenocortical carcinoma and a ganglioneuroblastoma. Further investigation showed a germline p53 mutation and Turner syndrome. It remains to be determined what effect the 45,X chromosomal complement may have on the expression of neoplasms seen in patients with p53 germline mutations.
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Keywords: adrenocortical carcinoma; ganglioneuroblastoma; Turner syndrome; p53 mutation

Division of Clinical Genetics, Department of Pediatrics, University of Tennessee, 711 Jefferson Avenue, Memphis, TN 38163, USA
E K Pivnick
G V N Velagaleti

Departments of Hematology/Oncology, St Jude Children's Research Hospital, Memphis, TN, USA
W L Furman
R C Ribeiro

Department of Pathology and Laboratory Medicine, St Jude Children's Research Hospital, Memphis, TN, USA
J J Jenkins

Pediatric Cardiology, Memphis, TN, USA
N A Chase

Correspondence to:
Dr Pivnick.

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Li-Fraumeni syndrome (LFS) is a rare autosomal dominant condition with incomplete penetrance that increases an affected person's risk of developing any of a variety of tumours.[1–5] Members of these families have an increased risk of childhood sarcoma, premenopausal breast cancer, leukaemia, brain tumours, osteosarcomas, and adrenocortical carcinomas.[2] Other tumours possibly associated with this syndrome include melanoma, carcinomas of lung, pancreas, and prostate, and gonadal germ cell tumours.[5] LFS was first described in 1969[1] and is associated with germline mutations of the tumour suppressor gene p53.[5–9] Although second malignant neoplasms have been described in children with p53 mutations,[7] two simultaneous but embryologically different tumours have not been reported previously.

We report the case of a 20 month old white female with a germline p53 mutation and Turner syndrome, who was diagnosed with both metastatic adrenocortical carcinoma and ganglioneuroblastoma.

Case report

The proband was born after 35 weeks of gestation to non-consanguineous, 28 year old, healthy, white parents. The family history was positive for colon and prostate cancer in three generations on the maternal side, and a benign brain tumour on the paternal side (fig 1). The pregnancy was uneventful and labour and delivery were uncomplicated. Birth weight, length, and head circumference were on the 40th centile. She had no unusual physical features (fig 2). During the first few months, failure to thrive owing to feeding difficulties was noted. Developmental milestones were normal. At 4 months of age she presented to the paediatric cardiologist with failure to thrive and

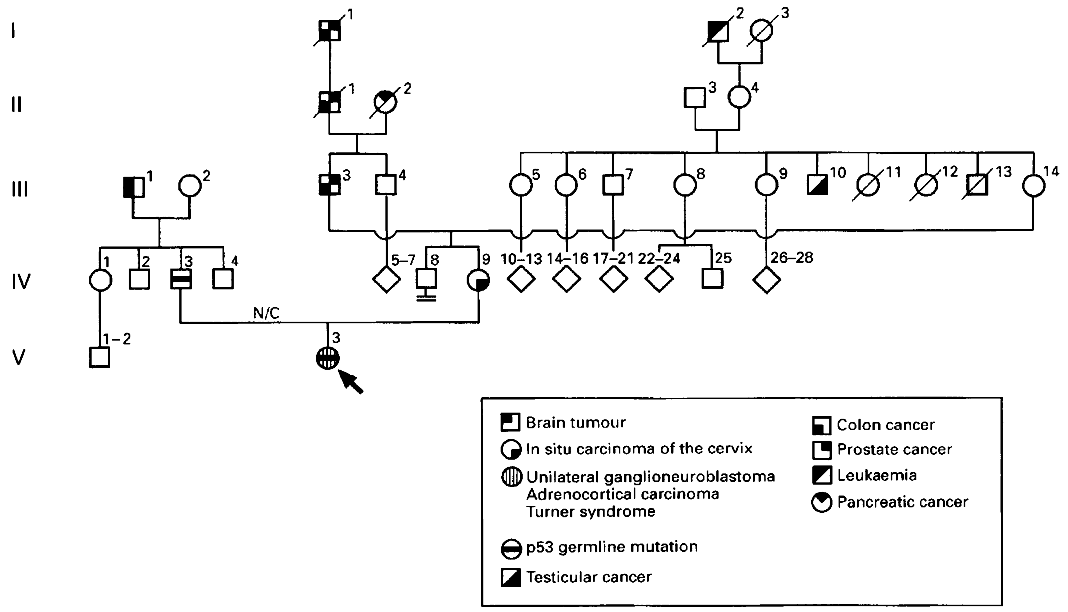

Figure 1 Partial pedigree of the family.

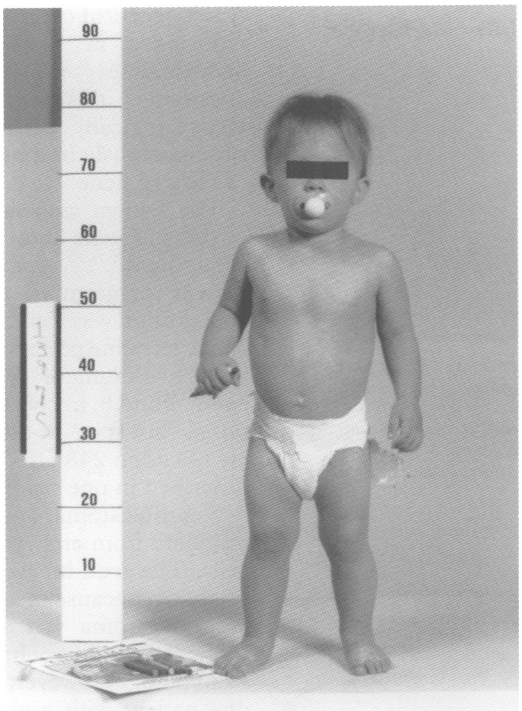

Figure 2 The proband at 21 months of age, height 80 cm (25th centile on normal growth curve). (Photograph reproduced with permission.)

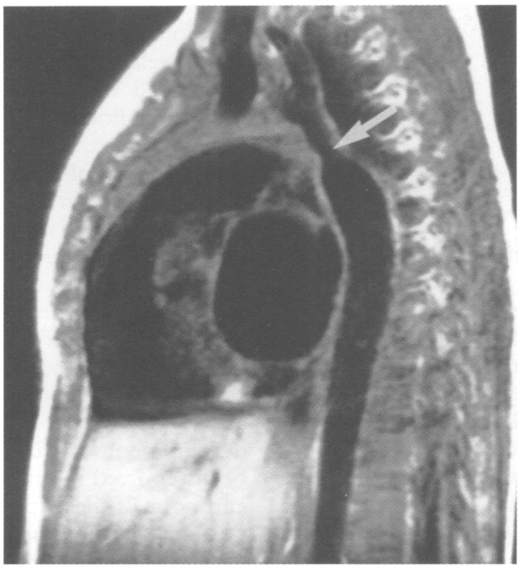

Figure 3 Magnetic resonance image of the chest with arrow showing coarctation of the aorta.

congestive heart failure from a high flow VSD, an abnormal non-stenotic mitral valve, and normal blood pressures with an irregular but not obstructive aortic isthmus. By 18 months she had differential pulses and sweating on exertion compatible with progressive coarctation and a VSD shunt. There was no history of paroxysmal sweating or flushing. After injection of contrast at cardiac catheterisation for mild Shone's complex (coarctation, parachute mitral valve, and bicuspid aortic valve)[10] and VSD, such a paroxysm did occur, prompting investigation for hypertension excessive for contrast or coarctation. A renal ultrasound showed a probable right adrenal mass. Computerised tomography (CT) and magnetic resonance imaging of the chest (fig 3) and abdomen (fig 4) showed a right pulmonary

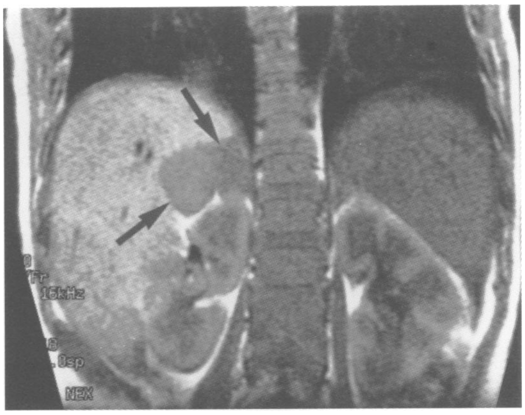

Figure 4 Selected magnetic resonance image of the abdomen with arrows showing two well defined, low density masses in the right suprarenal region. The larger was approximately 1.8 cm in maximum diameter and had no internal calcifications. The second measured approximately 1.5 cm and had flecks of calcium within it.

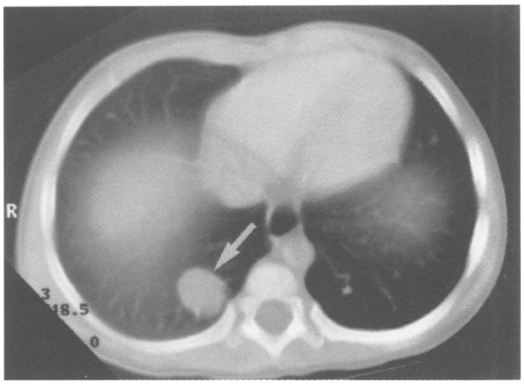

Figure 5 Selected CT image of the chest with arrow showing a well defined, round intermediate density in the right lower lobe measuring approximately 2 cm in diameter.

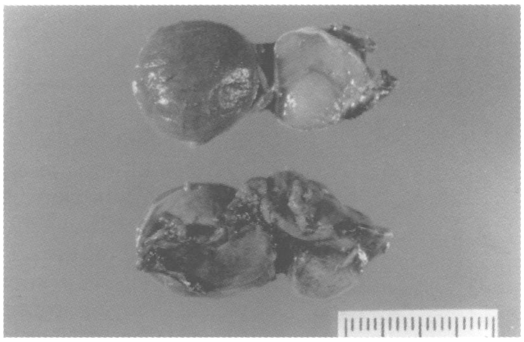

Figure 6 Adrenal gland containing two separate nodules of different colour and texture. The cut surface of the larger nodule is a uniform light orange-brown (darker nodule in the photograph), while the cut surface of the smaller is pale tan (lighter nodule) with tiny foci of chalky white calcification.

nodule (fig 5) and a right adrenal mass, respectively. A CT scan of the head, neck, and pelvis was normal, as was a bone scan. Microscopic examination of the bone marrow aspirate obtained from both iliac crests was normal. A laparotomy followed by a thoracotomy resulted in complete resection of the tumour and showed two histologically distinct right adrenal tumours: adrenocortical carcinoma (ACC) and ganglioneuroblastoma (GNB) with the former metastasising to the lung (figs 6, 7, and 8). Serum chemistries and complete blood count values were within normal limits except for a mildly raised serum lactate dehydrogenase 1099 IU/l (normal 420-920). Examination of

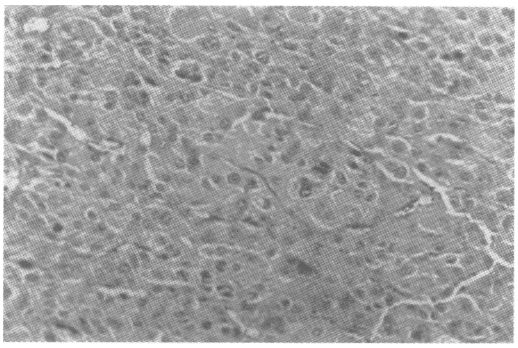

Figure 7 Photomicrograph of the light orange-brown nodule (darker nodule in fig 6) (adrenocortical carcinoma), containing large, epithelioid, extremely pleiomorphic cells, many of which are multinucleated. Cytoplasm is abundant and lightly eosinophilic with a suggestion of fine granularity. Mitotic figures are numerous and some are abnormal. Necrosis is absent.

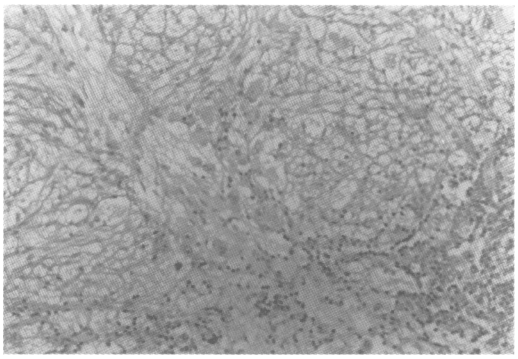

Figure 8 Photomicrograph of the pale tan nodule (lighter nodule in fig 6) (ganglioneuroblastoma), composed of nests of small neuroblasts plus larger maturing neuroblasts, all embedded in a fine neurofibrillary matrix. In other zones, larger maturing neuroblasts and fully mature ganglion cells are embedded in a schwannian spindle cell matrix. Focal calcification and a lymphocytic infiltrate are also present.

the urine for vanillylmandelic acid (VMA) and homovanillic acid (HVA) was within normal limits for age. There were no features of hyperadrenalism, virilisation, or Cushing's syndrome and her bone age was normal.

At 21 months of age cytogenetic analysis of the blood and skin fibroblasts showed a 45,X karyotype with no mosaicism detected. Mutation analysis of the p53 gene in blood showed a single base substitution in codon 248 of exon 7 which changed arginine (CGG) to tryptophan (TGG). The patient at 38 months of age is free of disease, 17+ months after the total resection of the adrenal tumours, the lung metastasis, and repair of coarctation. No specific treatment other than surgery for the adrenocortical carcinoma and the ganglioneuroblastoma was administered.

DNA isolated from leucocytes of the patient's parents were screened for the presence of a p53 mutation and the father was found to have an identical mutation. Blood samples from the paternal grandfather and other family members at risk were not available for study.

Discussion

The patient described here had two constitutional genetic abnormalities, Turner syndrome and a germline mutation of the p53 gene, and two simultaneous but different tumours, localised ganglioneuroblastoma and metastatic non-functioning adrenocortical carcinoma. Adrenocortical carcinoma has been previously reported in association with p53 abnormalities.[11 12] However, to the best of our knowledge, this is the first report of two embryologically distinct tumours occurring simultaneously in a patient with abnormalities of the p53 gene.

The known association between mutations of the p53 gene and childhood adrenocortical carcinoma[5 6 11 12] prompted us to examine our patient for germline p53 mutations. A single substitution was found at codon 248 of exon 7. Most germline p53 mutations found in patients with Li-Fraumeni syndrome occur between exons 5 and 8, in codons 110 to 307.[13] A mutational "hot spot" at the CpG dinucleotide moiety of codon 248 affected four of eight families described in one report.[6]

Neuroblastomas and ganglioneuroblastomas originate from embryonic neural crest derived cells. The true incidence of these tumours is unknown because many spontaneously regress. Neuroblastoma was not documented in the original families characterised by Li and Fraumeni.[1] However, Malkin *et al*[7] reported one patient with a germline p53 mutation in codon 248 who developed breast cancer after surviving neuroblastoma at 1 year of age. Davidoff *et al*[14] examined five neuroblastoma derived cell lines for p53 protein expression and found that four of these lines expressed high levels of this protein. The p53 gene was sequenced between codons 125 and 290 in these four lines and found to be normal wild type sequence. The authors surmised that this high level of p53 expression may reflect the embryonic origin of these tumours. No relation between the transformation of these cell lines and p53 could be determined. To our knowledge, p53 mutations have not been reported in isolated cases of neuroblastoma.

A number of investigators have suggested an association between neuroblastoma and conotruncal defects of the heart on the basis of aberrant neural crest migration and development.[15 16] However, this association has been reported in only about 20 previous cases and none of these have had coarctation as part of their cardiovascular anomalies.[16] On the other hand, coarctation has been a well described anomaly associated with sex chromosome aneuploidy.[17-20] A similar embryological basis for these cardiovascular anomalies in patients with TS has been proposed.[21] In our particular patient, neuroblastoma, TS, and coarctation may be interrelated.

Turner syndrome (TS), a heterogeneous clinical syndrome defined by partial or complete monosomy of the X chromosome, is found in approximately 1 in 2100 newborn girls.[22] However, pathognomonic clinical features are often not present and patients are then not diagnosed in infancy because of a normal phenotype.[23] The phenotype usually includes webbed neck, low posterior hair line, cubitus valgus, short stature, and lymphoedema.[23] Our patient had no phenotypic abnormalities other than a complex cardiac malformation that included coarctation and a history of failure to thrive.

TS has been associated with various tumours of the reproductive system, but has not been reported in association with Li-Fraumeni syndrome. Gonadoblastoma, one of the most common tumours in girls with TS, occurs almost exclusively in those who are mosaic for a Y chromosome.[24–26] Extragonadal neoplasm in TS has been sporadically reported.[27] The incidence of neurogenic tumours, such as neuroblastoma, ganglioneuroblastoma, and malignant melanoma, has been considered to be increased in TS.[27] However, published reports are too few to establish a definite relationship.[28]

It was challenging to devise a treatment plan for an infant with two potentially lethal tumours. Definitive treatment for metastatic childhood adrenocortical carcinoma has not been established. Prognostic factor analyses have indicated that children with small localised tumours have an excellent outcome,[29–31] and complete surgical resection remains the single most effective therapy. Chemotherapy with mitotane [1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)-ethane], or o,p'-DDD, an insecticide derivative that produces adrenocortical necrosis, has been used for inoperable adrenocortical carcinomas, but its efficacy in children is not known.[29–33] Although our patient had metastatic disease, complete resection of the primary tumour and the single pulmonary nodule rendered her free of disease. Stage I ganglioneuroblastoma in children below the age of 1 year carries an excellent prognosis. Surgery alone is associated with prolonged disease free survival in more than 90% of cases.[34] Therefore, we chose surgery as the only treatment for this patient. She remains clinically well and free of disease 17+ months after the diagnosis.

Our patient's family further shows that a high index of suspicion is needed to detect a family cancer syndrome, especially when only a limited portion of the family history is known, or when a child is the first family member to develop a cancer. Our patient inherited the p53 mutation from her father, who had no clinical evidence of cancer at the time of diagnosis of cancer in his daughter. The onset of malignancy in a patient who has a p53 mutation is thought to depend on the stochastic acquisition of sufficient additional genetic abnormalities to give rise to a malignant clone.[7] Thus, a child may develop a malignancy before the affected parent or other affected first degree relatives.

The Li-Fraumeni syndrome is a devastating disorder in which affected members have as much as a 20-fold relative risk of developing certain kinds of cancer.[33] About half the cancers that occur in Li-Fraumeni families occur in family members less than 30 years old.[36] Although the risk appears to decrease with increasing age,[35] lifelong surveillance in affected patients should be continued. This patient's presentation with two embryologically different tumours, one of which is not typically associated with p53 mutations, was highly unusual. Numerous X linked genes, some of which escape X chromosome inactivation, are potentially involved in oncogenesis.[37 38] The loss of one or more of these genes may underlie the relationship between TS and malignancy.[39] It is possible that TS ("first hit") unmasked an abnormality in an X linked tumour suppressor gene ("second hit").

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