Chromosomes of metastatic retinoblastoma

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SUMMARY Chromosomal abnormalities were detected in the bone marrow of a girl with disseminated retinoblastoma. One of these abnormalities, $i(6p)$, is characteristic of primary retinoblastoma and its presence confirmed the diagnosis of bone marrow infiltration with retinoblastoma. This approach could be extended to study other tumours of childhood.

Characteristic chromosomal abnormalities have been described in primary retinoblastoma cells.¹⁻⁴ The availability of fresh tumour tissue for such investigations, however, is limited, not least by the traditional practice of immediate fixation of the enucleated eye so that accurate staging of the tumour can be achieved. Disseminated retinoblastoma with involvement of the bone marrow is rare. Nevertheless, when this pattern of disease occurs it provides the opportunity to examine directly the karyotype of the tumour cells.

Monoclonal antibodies are of value in determining the tissue of origin of metastatic disease, and specific cytogenetic abnormalities may also be of help. We report the karyotypic abnormalities of metastatic cells in a child with retinoblastoma who developed bone marrow infiltration.

Case report

A girl, aged 2 years and 5 months, whose unilateral retinoblastoma had been enucleated one year previously, presented with three hard lumps on her head. There was no family history of retinoblastoma

and her sibling's eyes were normal. Apart from these lumps and the enucleation, physical examination, including that of the opposite eye, yielded entirely normal results. A bone scan showed areas of increased uptake in the skull. A blood count showed haemoglobin 9.3 g/dl, white blood cell count $6.7 \times 10^9/l$ (30% neutrophils, 65% lymphocytes, and 5% monocytes), and platelets $90 \times 10^9/l$. Ultrasound examination of her abdomen produced normal results. There were no intracranial abnormalities on computed tomography of her head.

Biopsy examination of one of the lumps on her head showed a primitive round cell tumour with small darkly staining cells and limited eosinophilic cytoplasm. In areas there were attempts at rosette formation. Examination of her bone marrow showed widespread infiltration with non-haemopoietic malignant cells, which resembled disseminated neuroblastoma. The malignant cells reacted with the monoclonal antibody UJ13A, which detects cells of neuroectodermal origin.⁵ Urinary excretion of vanillylmandelic acid was normal. The cerebrospinal fluid did not contain malignant cells. A diagnosis of disseminated retinoblastoma with bone marrow involvement was made. Peripheral blood esterase D activity was normal. She was treated with vincristine, cis-platinum, teniposide, and cyclophosphamide (OPEC). Although there was initial clearing of malignant cells from the bone marrow, she died nine months later from recurrent disease.

Chromosome analysis of bone marrow derived metaphases showed two cell lines; three cells had an apparently normal 46,XX karyotype and three represented an abnormal clone with a modal num-

Figure Partial karyotype, showing trisomy 1q, 2q+, 5q-, $i(6p)$, 7q-, and a marker chromosome.

ber of 45 chromosomes. Consistent anomalies were trisomy 1q, 2q+, 5q-, 7q-, an unidentified marker chromosome, and tetrasomy of the short arm of chromosome 6, manifest as an additional isochromosome, i(6p) (Figure). Some random chromosome loss was evident.

Discussion

Though it only rarely occurs, retinoblastoma is known to disseminate to the bone marrow. The occurrence of the malignant cells in the bone marrow and their reactivity with UJ13A were highly suggestive of a neuroectodermal origin. Second primary tumours have been described in patients with hereditary bilateral forms of retinoblastoma, although they usually occur much later than this. Neuroblastoma, primitive neuroectodermal tumour, and medulloblastoma, also derived from neuroectodermal tissue, are not recognised, however, as characteristic second malignant neoplasms in these patients. In addition, the absence of either an intracranial mass lesion or an abdominal tumour and a normal urinary excretion of vanillylmandelic acid made a diagnosis of medulloblastoma or neuroblastoma unlikely. Primitive neuroectodermal tumours, unlike neuroblastoma, rarely involve the bone marrow. The evidence that this disseminated tumour was retinoblastoma is compelling.

The presence of large numbers of dividing retinoblastoma cells in such a readily accessible tissue provided the rare opportunity to obtain direct chromosome preparations and compare any abnormalities with reports of those obtained from fresh primary tumour tissue.

This is only the second report of the karyotypic abnormalities of metastatic retinoblastoma. Benedict *et al* described trisomy 1q, i(6p), and an interstitial deletion of 13q in cells from a rib metastasis.¹ These three are the most common abnormalities in cases of primary retinoblastomas,¹⁻⁴ two of which, i(6p) and trisomy 1q, were found in the metastatic cells in our patient. The additional abnormalities 2q+, 5q-, 7q-, and the marker chromosome may reflect more malignant growth characteristics of the metastatic cells of this

tumour. The presence of two macroscopically normal chromosomes 13 is consistent with a sporadic, non-hereditary form of retinoblastoma, which is supported by the normal esterase D activity.⁶

Although trisomy 1q is not specific for retinoblastoma, the similarities between the chromosomal abnormalities in the metastatic cells in our patient and those described in primary tumours, particularly the presence of i(6p), encourages the use of cytogenetic investigations to confirm the identity of metastatic deposits in this disease. This case illustrates the relative ease with which such information can be obtained. Clearly, this approach could be extended to the study of other tumours of childhood.

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