Anaplastic large cell lymphoma with the t(2;5)(p23;q35) NPM/ALK chromosomal translocation and duplication of the short arm of the non-translocated chromosome 2 involving the full length of the ALK gene

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translocation. However, in this case the size of the malignant cells was larger than is usually seen in common type anaplastic large cell lymphoma.

The cytogenetic study displayed the following tetraploid karyotype: 94,XXYY,+X,+Y, t(2;5)(p23;q35)×2,ish t(2;5)(ALK+;ALK+)×2, dup(2)(p11;p25)×2.ish dup(2)(ALK++)×2, +5, add (8)(p23)×2, I(17)(q10) (fig 1). The four copies of chromosome 2 were abnormal. Two of them resulted from a standard t(2;5) translocation and had the characteristic aspect of the derivatives 2 generated by t(2;5). The cytogenetic aspect was confirmed by in situ hybridisation with the Vysis LSI ALK probe (Ref 32-190069). This probe contains two fragments located on each side of the breakpoint at 2p23: a 5' centromeric fragment (green signal) remains on the der(2); derivatives resulting from the t(2;5) translocation. Two copies of the ALK gene (indicated as dup ALK) are present on the two copies of dup(2)(p11p25). Two copies of the der(2), of the der(5), and of the dup ALK are seen because of tetraploidy.

The process by which the t(2;5)(p23;q35) translocation transforms cells is not known. However, despite the fact that there are some anaplastic large cell lymphoma cases that are negative for this translocation,1 in vivo and in vitro models have provided evidence that this cytogenetic abnormality is by itself oncogenic.4,5 The ALK protein, the normal functions of which have yet to be elucidated, is expressed in rare cases of non-anaplastic large cell lymphoma and in a few normal tissues.8 Theoretically, this protein functions as a tyrosine kinase receptor but its ligand remains unknown.8 So far, the activation of the tyrosine kinase domain of ALK has been shown to be the consequence of the gene rearrangement.7 The chromosomal partners isolated to date, namely NPM and TPM3, are proteins with dimerisation domains, enabling the formation of NPM/ALK and TMP3/ALK homodimers, and thereby allowing the activation/autophosphorylation of the TK domain of ALK.7 So far, numerical abnormalities of the normal ALK gene have not been demonstrated. We describe herein a case of anaplastic large cell lymphoma with four copies of the normal ALK gene and two copies of the t(2;5)(p23;q35) translocation. The cytogenetic pattern suggests that these structural abnormalities occurred before the cells became tetraploid. Regarding ALK expression, our data show that the normal ALK gene, even in multiple copies, remains silent and that only the chimaeric NPM/ALK (80 kDa) and not the full length ALK protein (200 kDa) was expressed (fig 2).

Figure 1 Results of hybridisation with the dual colour ALK probe on metaphase chromosomes. The Vysis LSI ALK probe contains two differently coloured probes labelling opposite sides of the breakpoint in the ALK gene found in the t(2;5) translocation. The telomeric fragment (red) is translocated on to the der(5) and the centromeric fragment (green signal) remains on the der(2); derivatives resulting from the t(2;5) translocation. Two copies of the ALK gene (indicated as dup ALK) are present on the two copies of dup(2)(p11p25). Two copies of the der(2), of the der(5), and of the dup ALK are seen because of tetraploidy.

Figure 2 Results of the western blot analysis with the ALK antibody. A band of 80 kDa corresponding to the molecular weight of the NPM/ALK fusion protein was found in 16 µg of protein extracts from the t(2;5) positive cell line SUDHL1 (lane 1) and in 40 µg and 60 µg (lanes 2 and 3, respectively) of protein extracts from the lymph node tumour. The 46 kDa band represents the actin protein used to assess the quantity of protein loaded into each lane.
Although based on a single case, these data indicate that structural rather than numerical abnormalities of the ALK gene are implicated in the pathogenesis of anaplastic large cell lymphomas.

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