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Anaplastic Lymphoma Kinase (ALK)

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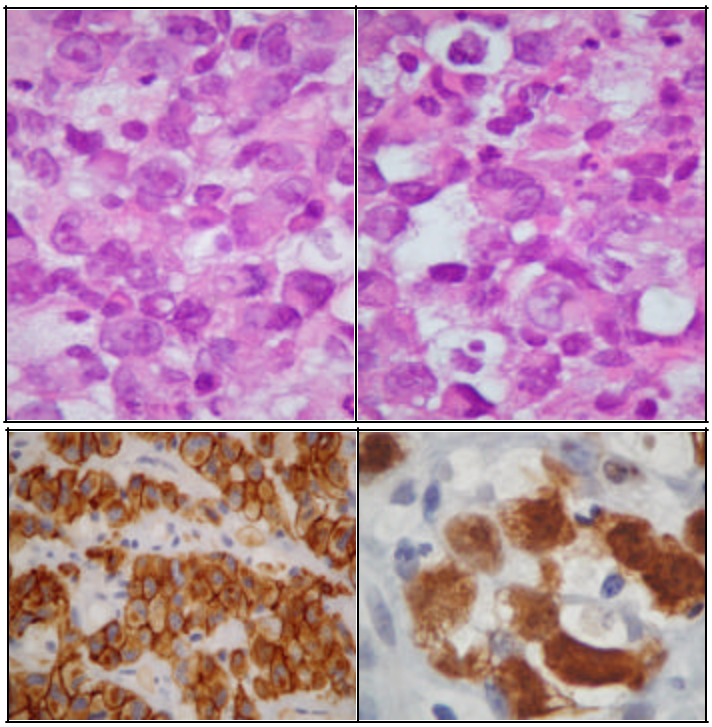
by Rodney T. Miller, M.D., Director of Immunohistochemistry

The anaplastic lymphomas kinase (ALK) gene is located on chromosome 2p23, and codes for a protein that is expressed in some cells of the central nervous system, but in virtually no other normal human cells. Interest in this protein among diagnostic pathologists has been related to its utility in recognizing a subset of CD30+ anaplastic large cell lymphomas (ALCL's), that show a characteristic t(2;5)(p23;q35) translocation. This translocation results in an abnormal fusion gene involving the ALK gene and the nucleophosmin (NPM) gene (located on chromosome 5q35), which codes for a ubiquitously expressed nucleolar phosphoprotein that functions in transporting components of ribosomes between the cytoplasm and nucleolus during the final stages of ribosome assembly. Transcription of this abnormal NPM-ALK fusion gene results in the production of an abnormal protein (called p80) that functions as a protein tyrosine kinase.

With the availability of a commercially available monoclonal antibody to the aberrantly expressed ALK protein (the ALK-1 antibody), it has been found that immunostains using the ALK-1 antibody are as effective as FISH testing for detecting ALK gene rearrangements in patients with CD30+ anaplastic large cell lymphoma (Cataldo et al). Identification of this protein is important, since ALK-1 positive anaplastic large cell lymphomas have a significantly better prognosis than ALK-1 negative cases (although Nagasaka et al found that this may not be the case when these tumors present in bone), and most authorities recommend that the presence or absence of ALK-1 immunoreactivity be reported in every case of CD30+ anaplastic large cell lymphoma.



70 y.o. female underwent needle biopsies of a retroperitoneal mass. H&E (top 2 photos) showed a pleomorphic large cell malignant tumor. Note the "hallmark" cell with the horseshoe-shaped nucleus in the center of the top right photo. The tumor cells were strongly positive for CD30 (Ki-1) (lower left) and showed strong nuclear and cytoplasmic reactivity with ALK-1 (bottom right). Nuclear reactivity with ALK-1 generally correlates well with the presence of the classic t(2;5)(p23;q35) translocation associated with many of these tumors.

Patients who have the characteristic t(2;5)(p23;q35) translocation typically show both nuclear and cytoplasmic staining with ALK-1 antibody, whereas those with variant translocations often show staining limited to the cytoplasm of the neoplastic cells. Gene rearrangement studies have shown that ALK-1 positive CD30+ ALCL's are typically T-cell neoplasms, although they may show a "null" phenotype on immunohistochemical analysis.

As more and more cases of CD30+ ALCL are studied, the morphologic spectrum of this entity has expanded significantly. The common type of ALCL (which comprises about 75% of cases) shows pleomorphic large cells with lobulated or horseshoe-shaped nuclei, the latter referred to as "hallmark" cells. The small cell variant is composed of cells with small nuclei and clear cytoplasm, often resulting in a morphologic resemblance to histiocytes or some cases of peripheral T-cell lymphoma that have cells with clear cytoplasm. A lymphohistiocytic variant has also been described, in which cells similar to those noted in the small cell variant are admixed with "hallmark" cells, growing in a background of numerous pale histiocytes, which may be so prominent as to obscure the neoplastic cells in some areas. Finally, a sarcomatoid variant is described that mimics a variety of soft tissue sarcomas.

A potentially confusing finding noted in 2 ALK-1 positive ALCL's that we have seen in the past several years has been the focal expression of low molecular weight cytokeratin by the neoplastic cells. (In one of these cases the diagnosis was confirmed using molecular techniques). Although ALK-1 positive ALCL's frequently express EMA, to our knowledge expression of cytokeratin in ALK-1 ALCL's has not yet been reported in the literature, although there is a report of low molecular weight cytokeratin expression in a case of B-cell ALCL (Frierson HF et al).

Immunohistochemical detection of the ALK-1 protein has also been reported in a number of other situations, including rare cases of CD30 negative large cell lymphomas and rare cases of large B-cell lymphoma (Reichard et al). Immunohistochemical expression of ALK-1 has also been reported in 28-62% of inflammatory myofibroblastic tumors. At the 2003 United States and Canadian Academy of Pathology meeting, a number of groups studied the expression of immunohistochemical expression of ALK-1 in a variety of mesenchymal lesions. Although the results varied somewhat, expression of ALK-1 was reported to be present in up to 40% of cases of malignant peripheral nerve sheath tumor, 19-22% cases of rhabdomyosarcoma, 10% of leiomyosarcomas, 9% of cases of MFH, 39% of neuroblastomas, and 22% of Ewing's/PNET.

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Rodney T. Miller, M.D.
Director of Immunohistochemistry
214-237-1631 • Fax 214-237-1770
rmiller@propathlab.com

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PROPATH
8267 Elmbrook Drive, Suite 100 • Dallas, Texas 75247-4009
214-638-2000 • Toll Free: 800-258-1253 • Fax: 214-905-3457
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