Pathogenesis and prognostic parameters in synovial sarcoma

J.M. Lopes

Dept. of Pathology Porto Cancer Center, Portugal.

Synovial sarcoma has two major histological subtypes: monophasic and biphasic, depending respectively on the absence or presence of solid/glandular cell components together with spindle cell areas. Synovial sarcoma accounts for about 10% of malignant soft tissue tumors, is most prevalent in adolescents and young adults, and arises frequently around the knee and ankle joints.

Synovial sarcoma is associated in more than 90% of cases with the chromosomal translocation t(X;18)(pll .2;qll .2) in both subtypes and in both solid/glandular and spindle cell components. As a result of this translocation, the SYT gene on chromosome 18 fuses either to the SSX1 or to the SSX2 gene on the X chromosome. A comparative genomic hybridization study of synovial sarcoma depicted more complex and numerous genetic changes in monophasic than in biphasic synovial sarcoma.

Synovial sarcoma can recur locally, usually within 2 years after diagnosis, and can metastasize to the lymph nodes and the lungs. The 5-year survival rate is around 50%. The prognosis of synovial sarcoma is influenced by the stage of the disease (as defined by the tumor node metastasis staging system), age (better in the pediatric group), site (better for distal tumors), extent of calcification (better for extensively calcified tumors), mitotic activity (better for tumors with low mitotic index), mast cell count (worse for tumors with low counts), necrosis (worse when more than 50% necrotic), rhabdoid cells (worse whenever present), proliferative index (worse for tumors with high proliferating cell nuclear antigen and Ki-67 labeling indices) and ploidy (worse for aneuploid tumors).

The histogenesis of synovial sarcoma is still controversial and there are several morphological (ultrastructural and immunohistochemical) features that suggest the possibility of either a primary carcinoma or carcinosarcoma of soft tissues.

When will cancer genetics and biology give us something clinically useful?

V.P. Collins

University of Cambridge, Addenbrooke's Hospital, Cambridge, UK.

The last 20 years have seen enormous advances in our knowledge of the molecular basis of cancer. As yet, little of this has resulted in major advances in cancer care (1). Cancer research does not occur against a background of known molecular mechanisms of cell growth control, control of apoptosis or control of differentiation. The normal processes have generally had to be worked out in parallel with the abnormalities of cancer cells. Our understanding of the molecular mechanisms involved in cancer has been, and probably still is, rudimentary. We have yet to begin to understand the complexity of these diseases at the molecular level. To date, some attempts have been made to use the new information obtained. Unfortunately, the majority of studies have, for practical reasons, been limited to the examination of one or two gene products in clinical material. For real advances, much more sophisticated approaches will be necessary to obtain clinically relevant information. It is unlikely that the expression, or lack of expression, ot single genes will give us clinically relevant and dependable information on which to base a choice of therapy and/or an assessment of prognosis. Current developments in the molecular area include microarrays (2), which should permit relatively high throughput and a molecular profiling of tumor specimens, as yet unparalleled. This can be utilized, both at the genetic and transcript levels. The combination of such technologies with microdissection techniques will no doubt provide much relevant data. However, there are initially two major problems with this approach: i) the huge amounts of data that can be produced must be possible to interpret and ii) high quality clinical information must be available on the cases studied to permit correlation to the molecular processes. This cannot be overemphasized.

High throughput mutation analysis still remains a technical problem. In addition, technology will not tell us the protein levels of the gene products in tumor cells. Further advances in methodologies quantitating specific proteins – preferably at the cellular level – will be required. Other interesting technological developments includes comparative genomic hybridization and spectral imaging. These technologies are not simple and further advances in computer assisted analysis will be necessary.

However, in some areas, these technologies are used, such as hematology (3). Cytogenetics, and more recently, interphase fluorescence *in situ* hybridization and polymerase chain reaction (PCR)-based clonality studies are becoming routine (3, 4). The identification of infectious agents, such as virus and bacteria, and even their resistance patterns can be carried out on histopathological material using mainly PCR-based methodologies. It is adequate that simple genomes should be the first to be routinely studied. However, with our present conceptual framework, the future looks very exciting and, while we must not minimize the problems, the potential is there for a relevant characterization of human tumor cells.

It is only when we truly understand the mechanisms involved in individual cancers that molecular profiling will become essential for determining the optimal therapy. When we have reached this point, the rational development of agents, which can replace, correct or disrupt the aberrant tumor cell will become possible. Some advances are already being made in this area, such as the identification of small molecular tyrosine kinase inhibitors.

When we consider the complexity of the cellular functions shown to be aberrant in tumor cells, it is not really surprising that this knowledge has not led to more clinical advances.

References

1. Kaye SB. *Perspective: Cancer care and the newbiology* J Pathol 1999; 187: 4-7.
2. Lander ES. *Array of hope.* Nat Ganat Supp 1999; 21: 3-4.
3. Greiner TC. *Commentary: Advances in molecular heematopathology - T-cell receptor and bcl-2 genes.* Am J Pathol 1999; 154(1): 7-9.
4. shipley J, *Fisher* C. *Editorial: Chromosome translocation in sarcomas and the analysis of paraffin-embedded material.* J Pethol 1998; 184: 1-3.