

Letters to the Editor

RAJANI B, SMITH TA, REITH JD, GOLDBLUM JR: RETROPERITONEAL LEIOMYOSARCOMAS UNASSOCIATED WITH THE GASTROINTESTINAL TRACT: A CLINICOPATHOLOGIC ANALYSIS OF 17 CASES. *MOD PATHOL* 1999;12:21–28.

To the Editor: In the interesting paper describing retroperitoneal leiomyosarcomas, Rajani *et al.* (1) mentioned repeatedly a concept of extra-gastrointestinal gastrointestinal stromal tumors, which should be differentiated from leiomyosarcomas. However, this concept appears to be questionable from a histogenetic point of view. Gastrointestinal stromal tumors (GIST) originate from interstitial cell of Cajal, *i.e.*, from the gastrointestinal pacemaker cell (more precisely: they differentiate toward this cell), as supported by several studies (2–4). The occurrence of the pacemaker cell in the retroperitoneum or in other extra-gastrointestinal sites was not described until now. Consequently, we do not know the origin of possible extra-gastrointestinal GIST. One may consider two explanations for this:

1. The origin of GIST is represented by any cell, which is more ubiquitous and different from the gastrointestinal tract-restricted pacemaker cell. Then, GIST might arise in the extra-gastrointestinal locations.
2. The origin of GIST is the pacemaker cell, and therefore extragastrointestinal GISTs do not exist; and some sarcomas in extra-gastrointestinal locations may only resemble GIST. This is supported also by the studies of multiple familial GIST (5, 6). These patients had multiple gastrointestinal lesions, but none of them had any extra-gastrointestinal GISTs, which would be interpretable as a part of the multiple neoplasia (neoplastic disease of the whole pacemaker cell system).

Thus, the existence of extra-gastrointestinal GIST seems to be uncertain.

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In reply: The concept of “extragastrointestinal stromal tumors” is a new one. Certainly, there have been ample data published over the past few years showing that most, if not all, gastrointestinal stromal tumors either originate from or differentiate toward interstitial cells of Cajal (1, 2). In 1996, Reith *et al.* (3) reported (in abstract form) an analysis of 39 tumors that arose in the abdominal cavity that histologically closely resembled gastrointestinal stromal tumors and were unassociated with the gastrointestinal tract. These tumors did not really resemble conventional spindle or epithelioid leiomyosarcomas that arise in the soft tissues. Immunohistochemical analysis revealed that 50% were CD34-positive, but all stained strongly for CD117 (*c-kit*), a marker of interstitial cells of Cajal and the single best marker of gastrointestinal stromal tumors. In addition, only a minority of these tumors expressed myogenic antigens. Thus, based upon the histologic and immunophenotypic similarities to gastrointestinal stromal tumors, the authors proposed the term “extragastrointestinal stromal tumor.”

With respect to the histogenesis of such tumors, several possibilities exist. First, these tumors may have arisen from the gastrointestinal tract but subsequently became detached to lie within the abdomen. It is also possible that these tumors arise from mesenchymal elements that have the ability to recapitulate the phenotype of interstitial cells of Cajal. Regardless of their histogenesis, we believe there is evidence to support the existence of tumors that are histologically and immunophenotypically

indistinguishable from gastrointestinal stromal tumors that arise in extragastrointestinal sites.

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CORRESPONDENCE RE: BRUNNING R: PROPOSED WHO CLASSIFICATION OF ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROMES. *MOD PATHOL* 1999;1:102–4.

To the Editor: We have read with interest the Myelodysplastic Syndromes (MDS) and Related Disorders program abstracts from the Society for Hematopathology, published in the January 1999 issue of *Modern Pathology*. In particular, the session entitled “Proposed WHO classification of MDS and MDS-related acute leukemias” (1) caught our attention.

Our group has been actively researching the acute erythroleukemias since the late 1980s. In this time, we have developed, and extensively published our classification, (2–8) as follows:

- acute erythroleukemia, M6a—traditional FAB-M6
- acute erythroleukemia, M6b—pure erythroleukemia
- acute erythroleukemia, M6c—mixed erythroleukemia

In addition, we have published abstracts and presented this classification at the International Academy of Pathology (9), International Society of Hematology, and the American Society of Hematology (10, 11) meetings, and our recommendations have also been cited in the recent literature (12, 13). Therefore, we are surprised to find the M6a and M6b subtypes to be reversed in the newly proposed WHO classification, and the M6c subtype to be completely overlooked. Although we suspect that the reversal of M6a and M6b is a typographical error, we believe it is important to set the record straight.

The established classification of acute erythroleukemias is based partly on the old FAB criteria and also upon morphologic, cytochemical, and immunophenotypic criteria (3). Namely, all bone marrow aspirates demonstrate $\geq 50\%$ erythrocytic precursors, with erythroid dysplasia. Dysplasia of the granulocytic and megakaryocytic cell lines may or may not be present. The M6a subtype is characterized by $\geq 30\%$ myeloblasts and/or monoblasts of the nonerythrocytic component (FAB exclusion criteria); the M6b subtype is defined as $\geq 30\%$ pronor-

moblasts of the erythrocytic elements; and the M6c subtype has $\geq 30\%$ blasts and $\geq 30\%$ pronormoblasts by the aforementioned exclusion criteria. As the dysplastic changes may, at times, make definitive categorization of the blasts as erythrocytic *versus* nonerythrocytic difficult, the morphologic features must always be confirmed by cytochemical stains, immunohistochemical stains, and/or flow cytometric analysis.

These three separate subtypes must be distinguished from one another, not for esthetic purposes, but in order to predict useful prognostic information for the clinician and the patient. When treated with standard myeloid protocol (*i.e.*, ara-C followed by daunorubicin), the M6a and M6c subtypes demonstrate a 100% remission rate, whereas the vast majority of M6b patients remain refractory to treatment. In addition, the M6c patients remain in remission for a significantly shorter time than the M6a group. Mean survival for these subtypes is: M6a 31.4 ± 32 months, M6b 3.15 ± 4.2 months, and M6c 10.5 ± 12.7 months.

The malignant clonal cell of origin, manifesting an acute erythroleukemia of any subtype, is not a myeloblast or pronormoblast, but appears to be a multipotential stem cell (4, 14, 15), which apparently shows varying degrees of erythrocytic and granulocytic lineage maturation. Therefore, the three distinct subtypes of acute erythroleukemia are not three separate diseases, but rather are manifestations of the same disease process. The poor remission rate and short survival characteristic of this disorder are dependent upon a number of factors, which include: a high pronormoblast to myeloblast ratio within diagnostic marrow aspirates (3), a high proliferative index (3), “unfavourable” cytogenetic aberrations (5), and a high incidence of the multidrug resistance phenotype (5).

Because acute erythroleukemia, M6a, was first reported by Di Guglielmo in 1917, and described by the

FAB group as FAB-M6, it was designated "A." Di Guglielmo then went on to describe the *disease* in 1926, which was not included in the original FAB classification. Logically and chronologically, this subtype was designated "B" (2). Finally and most recently, a mixed erythroleukemia was described and was designated "C" (3). The real importance of this issue is in the recognition of the distinct subtypes and application of appropriate treatment.

As our group has had extensive experience with this rare and aggressive disorder, we would certainly be delighted to share our extensive collection of data with the World Health Organization committee, and also to respond to any further questions that may arise.

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