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# LETTER TO THE EDITOR

To the Editor:

We were heartened by the recent report from Tamborini et al (2002) that described their demonstration of the SYT-SSX fusion transcript in a small percentage of cases originally diagnosed as malignant peripheral nerve sheath tumors (MPNST). Our interest in their study stems from the fact that the data in their report show the same trend as that of our recent study (O'Sullivan et al, 2000), as well as data of other groups (Hiraga et al, 1998; Naito et al, 2000; Vang et al, 2000). In these studies, the data show that RT-PCR testing demonstrates the SYT-SSX fusion transcript in a subset of cases that are diagnosed as MPNSTs by established morphologic and immunohistochemical methods. What separates the studies is the interpretation of these experimental results.

In the reports by Tamborini et al (2002) and others (Hiraga et al, 1998; Naito et al, 2000), MPNSTs that were shown to harbor SYT-SSX fusion transcripts were subsequently reclassified as synovial sarcoma (SS) on the basis of the view that the t(X;18) is 100% specific for SS, despite that the cases were accepted as *bona fide* examples of MPNST at the initiation of the studies. Some groups have summarily reclassified the cases that harbor an SYT-SSX fusion transcript as SS (Hiraga et al, 1998; Naito et al, 2000). Tamborini et al (2002) admittedly provided more information on the problematic cases, but their unblinded retrospective review of only those cases with an unexpected RT-PCR result is a form of discrepant analysis, an intrinsically flawed and biased method for evaluating test specificity (Hadgu, 1999; Miller, 1998). Furthermore, their criteria for amending the diagnoses are ad hoc, and it is uncertain whether these criteria would have allowed them to identify the cases that harbored SYT-SSX transcripts had all their cases been submitted to blinded review. What is noteworthy, however, is that these morphologic criteria were still insufficient to allow for definitive reclassification of one of their cases (their case 18), for which the presence of the SYT-SSX transcript itself was interpreted as evidence to justify the amended diagnosis. It is a circular argument: The t(X;18) is presumed to be 100% specific for SS; cases of MPNST that harbor an SYT-SSX fusion transcript are reclassified as SS (where the presence of the SYT-SSX fusion transcript itself is justification for reclassification); the 100% specificity of t(X;18) for SS is thereby simultaneously confirmed and perpetuated.

In our study (O'Sullivan et al, 2000) and in those of others (Vang et al, 2000), cases that were originally diagnosed as MPNST but that were found to harbor an SYT-SSX fusion transcript were interpreted as evidence of tumors in which there is discordance between the morphologic and genetic findings. In our report, we were concerned with the methodologic problems introduced by retrospective reclassification of cases that were accepted as MPNST by expert and experienced pathologists at the initiation of the study (O'Sullivan et al, 2000). However, had we chosen to interpret the finding of SYT-SSX fusion transcripts in these MPNSTs as evidence of misdiagnosed SS, we and Tamborini would be in agreement. Similarly, had Tamborini et al (2002) interpreted their finding of SYT-SSX fusion transcripts in MPNSTs as evidence that the t(X;18) translocation may not be 100% specific for SS, we again would be in agreement. What is clear is that Tamborini et al (2002) and others, including ourselves, share the same experimental result and that it is only the interpretation of the result that differs.

The lively debate concerning the most appropriate interpretation of the data will continue until prospective, randomized clinical trials demonstrate that, for cases with discordant morphologic and molecular findings, genetic diagnoses more accurately predict patient outcome than morphologic diagnoses (or vice versa). Until such data are available, we can take some solace in the fact that such discordant cases are uncommon; in fact, far more pathologists have weighed into this debate than there are extant discordant cases.

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Vang R, Biddle DA, Harrison WR, Heck K, and Cooley LD (2000). Malignant peripheral nerve sheath tumor with a t(X;18). Arch Pathol Lab Med 124:864–867.

Dear Editor:

It is surprising that the authors in their letter totally disregarded the main message of our investigation (Tamborini et al, 2002). Focusing on a single case (case 18), where the genotype did not completely fit with the morphology, through very peculiar speculations, they reached the conclusion that the difference between the "experimental" results obtained by us and other groups and their own (O'Sullivan et al, 2000), lies on the "interpretation."

We disagree with the authors' conclusion, which is in keeping with the final statement of their reply letter published in the July issue of Modern Pathology: "We would render the diagnosis of MPNST for a malignant spindle cell tumor arising in a nerve in a patient with NF1. . .even if the tumor were shown to harbor t(X;18)" (O'Sullivan et al, 2001).

Our investigation, prompted by their unexpected demonstration of t(X;18) in 15 (75%) of 20 of MPNSTs (Tamborini et al, 2002), clearly showed that MPNSTs do not share this translocation with SS and that the 2 (5.1%) of 34 cases that carried this hallmark were both miscategorized SSs, one of which had unusual MPNST-featuring morphology.

We purposely disregard the authors' provocative comments on our case material, which we consider suitable to verify the authors' results, being mainly made up of clinically, morphologically, and molecularly selected MPNSTs (Tamborini et al, 2002), of which more than one half were represented by NF1 cases. Otherwise, our results are confirmed by 141 additional cases analyzed by karyotyping or RT-PCR on frozen material in five different laboratories around the world (Landani et al, 2001).

Finally, we would like to spend some words about the "lively debate" regarding the "uncommon" occurrence of cases with "discordant morphology and molecular findings" and about which of the two features "more accurately predict patient outcome." Concerning the inconsistency between morphology and genotyping, in our experience and in the quoted literature, this phenomenon involves untreated and post-treated tumors and raises diagnostic problems that may be successfully overcome through the integration of both morphologic and molecular analyses (Barr et al, 1995; Knezevich et al, 1998; Maeda et al, 1998; Mezzelani et al, 1998; Naguera et al, 1998; Thorner et al, 1996). As to the outcome, recent preliminary findings in untreated sarcomas suggest that the disease outcome is driven by the genotyping rather than by morphology (Folpe and Weiss, 2002; Pilotti et al, 2000). Moreover, according to current understanding, genotype and morphologic phenotype both are powerful determinants for a tailored tumor management and thus outcome prediction. Similar to breast and head and neck carcinomas, primary chemotherapy started to be introduced into sarcoma-treatment schemes. In treated cases the disease outcome may be significantly modified according to the drug disease sensitivity. Besides few specific tumor-targeting treatments, such as STI 571 in GISTs, the schemes applied are conventional chemotherapy based. In line with recently published data (Johnstone et al, 2002), knowledge about tumor gene profile, in addition to drug mechanism of action, will become determinant for choosing effective treatments. However, this emerging role of genotype will not withdraw any power to the morphology that remains the milestone for categorization and natural history prediction of diseases.

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