Desmoid-Type Fibromatosis

TO THE EDITOR: We read with interest the article by Seinfeld et al. (Seinfeld J, Kleinschmidt-Demasters BK, Tayal S, Lillehei KO: Desmoid-type fibromatoses involving the brachial plexus: treatment options and assessment of c-KIT mutational status. J Neurosurg 104:749–756, May, 2006), because we have recently treated one patient with refractory supraclavicular fibromatosis who harbored a KIT exon 10 mutation and responded to imatinib. We would like to share our experience by presenting additional analyses, in which a durable activity of imatinib (major response still ongoing after 16 months of treatment) and a potential role for the stem cell factor (SCF)/KIT pathway in disease and sensitivity to imatinib are suggested.

Abstract

Object. Desmoid-type fibromatoses are a locally invasive soft-tissue lesion that is most commonly encountered in abdominal sites. The tumor also affects head and neck areas, particularly the supraclavicular region, where it may encase and distort the brachial plexus and compromise neurovascular structures. Neurosurgeons may be called on to treat desmoid-type fibromatoses in these sites. The authors describe their experience in treating four patients with desmoid-type fibromatoses involving the brachial plexus and report the results of immunohistochemical analysis of the tumors.

Methods. Gross-total excision with nerve sparing was the first-line therapy of choice, although the surgery was challenging. Intraoperative identification of the site of tumor origin from musculoponeurotic tissues by the neurosurgeon was necessary in two of the four cases to achieve a correct frozen section or final pathological diagnosis. Immunostaining for c-KIT (CD117) was undertaken in all cases in light of a previous report of positive CD117 immunoreactivity in abdominal desmoid-type fibromatoses. All four tumors manifested weak focal immunostaining for c-KIT. One of the patients was given adjuvant imatinib mesylate therapy, with limited success. Subsequent polymerase chain reaction testing revealed that three of the four tumors manifested a single base pair change in exon 10 of the c-KIT gene (A to C in two cases and A to G in one case). There was local recurrence in three patients, despite gross-total excision. With the combination of surgery and radiation therapy, local disease control was achieved in three of the four patients.

Conclusions. This represents the first report of c-KIT sequencing in desmoid-type fibromatoses and suggests a possible biological basis for continuing to explore the use of adjuvant imatinib mesylate therapy.

Desmoid-type or aggressive fibromatoses involving the brachial plexus represent a therapeutic challenge for clinicians. Indeed, complete excision, sometimes followed by radiotherapy, may damage crucial neurovascular structures, including the brachial plexus, thus inducing significant morbidity. In that case as well as in advanced disease, alternative complementary strategies are required. Systemic therapies such as hormone therapy, nonsteroidal antiinflammatory drugs, and conventional chemotherapy may induce responses. Recently, responses to the imatinib mesylate tyrosine kinase inhibitor Gleevec (Novartis) were reported in refractory aggressive fibromatosis. None of the treated tumors was in a supraclavicular location.

We recently reported a case of advanced cervicothoracic aggressive fibromatosis that involved the brachial plexus. The patient, a 33-year-old woman, first received tamoxifen without success and then underwent complete surgical removal of the tumor. One year later, a large cervicothoracic recurrence was documented and treated by subtotal resection, followed by luteinizing hormone-releasing hormone analogous therapy. Radiotherapy was considered potentially too highly toxic to be used. After 6 years of hormone therapy, a second cervicothoracic progression occurred. Because of KIT expression on immunohistochemical studies, imatinib was started at 400 mg/day. Evaluation after 10 weeks of treatment showed tumor progression, and the dose was increased to 600 mg/day. After 10 weeks, a minimal response was observed (31% decrease; World Health Organization criteria) which improved later. As of this writing, with a longer follow-up duration (after 16 months of treatment), the response is major (80% decrease) and is still ongoing. To our knowledge, this is the first case of supraclavicular aggressive fibromatosis that was sensitive to imatinib.

Interestingly, we identified at the DNA and RNA levels a heterozygote variant in KIT exon 10 (point mutation 1621A→C, resulting in the amino acid substitution Met541Leu) similar to that identified in two patients by Seinfeld et al. We also found this variant in blood leukocytes, suggesting its germinal origin. Few data exist in the literature regarding the molecular status of aggressive fibromatosis. Heinrich et al. found no mutation of KIT (exons 9, 11–13, and 17, but not exon 10, were sequenced) and platelet-derived growth factor receptor-α ([PDGFRα]; exons 12, 14, and 18) in 19 samples of aggressive fibromatoses. The interim analysis of the Sarcoma Alliance for Research through Collaboration trial of imatinib in advanced aggressive fibromatosis reported the existence of PDGFRα exon 18 polymorphisms/mutations. The significance of the Met541Leu KIT variant, which has since been described in other tissues and tumors, remains controversial: it may be either a polymorphism or a mutation with impact in human diseases such as chronic myeloid leukaemia, liposarcoma, and mastocytosis (Dubreuil et al., unpublished results). We identified this variant at the RNA level in biopsy samples of diseased skin obtained in 31 (18.3%) of 169 patients with mastocytosis, but in the genomic DNA of only one (1.5%) of 71 healthy participants (p < 0.005), and in none of the blood cell samples obtained in 10 patients in whom the Met541Leu variant was identified in tumor tissues, suggesting that it may represent a true somatic event.

To further address functional aspects of the KIT exon 10 variant, we examined cell models transfected with human wild-type (WT) or Met541Leu KIT produced by site-directed mutagenesis. No basal receptor tyrosine phosphorylation was observed. The response to a high dose of KIT ligand SCF was similar, suggesting that Met541Leu KIT is functional, although a previous study showed that the murine Met540Leu KIT variant, equivalent to the human Met541Leu variant, was more sensitive than WT KIT to...
stimulation by low doses of SCF. We also showed that the sensitivity to imatinib was similar in variant- and WT-KIT–transfected cells stimulated by SCF in terms of growth and KIT phosphorylation inhibition (Fig. 1).

We further analyzed our clinical tumor sample at the molecular level. Immunohistochemical studies showed positive staining of tumor cells for KIT (clone A4502; 1:50 dilution, Dako), but also a strong and diffuse staining for SCF from which we infer a possible autocrine mechanism of KIT stimulation (Fig. 2A). Western blot analysis of protein lysates (Fig. 2B) confirmed the strong positivity for SCF, and showed negativity for phosphorylated PDGFRα. Immunoprecipitation with anti-KIT antibody followed by Western blot analysis with antiphosphotyrosine antibody (Fig. 2C) showed that the Met541Leu KIT phosphorylation was present, but relatively weak compared with the KIT phosphorylation resulting from an intrinsic oncogenic mutation (exon 11) in a control gastrointestinal stromal tumor (GIST) sample. Thus, despite overexpression of SCF in the sample, there was minimal KIT phosphorylation. Similar findings have been described in dermatofibrosarcoma protuberans, another disease with high sensitivity to imatinib, in which only a relatively weak phosphorylation of PDGFRα results from PDGFβ autocrine stimulation. Recently, an autocrine/paracrine mechanism has also been suggested as an alternative and/or complementary mechanism of KIT activation in GISTs.

Based on our data, we suggest that there is durable activity for imatinib in refractory supraclavicular aggressive fibromatosis. Such activity, coupled with the identification of Met541Leu KIT variant and/or the abundance of SCF in our patient’s tumor, implies a potential role for the SCF/KIT pathway in aggressive fibromatosis as well as sensitivity to imatinib. Our results show that the exon 10 mutation is not activating or inactivating. Alternative explanations include an autocrine mechanism, eventually associated with a hypersensitivity to SCF related to the induction of ligand-independent dimerization induced by exon 10 mutation. These data need to be confirmed in a large series, notably to explore and search for correlations between activity of imatinib in aggressive fibromatosis and these molecular hypotheses. We suggest a more exhaustive series, notably to explore and search for correlations between activity of imatinib in aggressive fibromatosis and these molecular hypotheses. We suggest a more exhaustive series, notably to explore and search for correlations between activity of imatinib in aggressive fibromatosis and these molecular hypotheses. We suggest a more exhaustive series, notably to explore and search for correlations between activity of imatinib in aggressive fibromatosis and these molecular hypotheses. We suggest a more exhaustive series, notably to explore and search for correlations between activity of imatinib in aggressive fibromatosis and these molecular hypotheses. We suggest a more exhaustive series, notably to explore and search for correlations between activity of imatinib in aggressive fibromatosis and these molecular hypotheses. We suggest a more exhaustive series, notably to explore and search for correlations between activity of imatinib in aggressive fibromatosis and these molecular hypotheses. We suggest a more exhaustive series, notably to explore and search for correlations between activity of imatinib in aggressive fibromatosis and these molecular hypotheses.