CORRESPONDENCE

Desmoid Tumors and Celecoxib with Sorafenib

TO THE EDITOR: We report the consecutive cases of two patients who had multiple recurrences of locally advanced desmoid tumors and for whom treatment with combined medical and surgical approaches had failed. Both patients then had a major objective response to treatment with a combination of celecoxib and sorafenib.

In 2007, a 46-year-old woman with familial adenomatous polyposis (Patient 1) presented with subcutaneous and abdominal desmoid tumors complicated by a duodenal fistula that required extensive surgery (for a brief case history, see the Supplementary Appendix, available with the full text of this letter at NEJM.org). Multiple medical treatments, evaluated at a national referral center for familial adenomatous polyposis, failed to control the disease, which recurred and appeared to worsen regularly. Successive treatments included 400 mg of celecoxib per day for 7 months, 400 mg of imatinib per day for 8 months, 800 mg of imatinib plus 400 mg of celecoxib per day for 9 months, four injections of 5 mg of bevacizumab per kilogram of body weight every 2 weeks, and 600 mg of sorafenib per day for 15 months. After the patient underwent laparoscopic surgery for an abdominal subcutaneous desmoid tumor in 2013, the rapid extension of a residual perigastric lesion was treated with a combination of 600 mg of sorafenib per day and 400 mg of celecoxib per day from January 2014 through April 2017. The perigastric tumor receded after 6 months of therapy and had been reduced by more than 90% after 1 year, with no recurrence (Fig. 1A and 1B). The only side effect reported was grade 2 skin toxicity, as described in the Common Terminology Criteria for Adverse Events from the National Cancer Institute.

The other case involved a 33-year-old woman with familial adenomatous polyposis who had an intraabdominal desmoid tumor with jejunal fistula that had required external drainage, with limited efficacy, since October 2015 (Patient 2; for a brief case history, see the Supplementary Appendix). A 2-month course of 40 mg of tamoxifen per day was interrupted because of a history of thrombosis, and a 4-month course of monotherapy with 400 mg of celecoxib per day yielded no reduction in tumor size. After evaluation by a multidisciplinary team, a combination of 600 mg of sorafenib per day and 400 mg of celecoxib per day was initiated in June 2016. After 2 months of treatment, computed tomography was performed to evaluate the cause of new abdominal pain and revealed a major increase in tumor necrosis; the tumor was later drained. The volume of the tumor had been reduced by more than 50%, and the drains were removed in December 2016 (Fig. 1C and 1D). The patient reported grade 1 alopecia and skin rash. She underwent surgery 2 weeks later for recurrent sepsis related to the jejunal fistula. Surgery confirmed necrosis and a major reduction in the size of the tumor. Limited resection of the small bowel was performed.

Desmoid tumors are rare, monoclonal, mesenchymatous proliferations associated with mutations in the adenomatous polyposis coli gene (*APC*) or the gene encoding beta-catenin (*CTNNB1*). These locally invasive tumors represent a major cause of death in the population with familial adenomatous polyposis, and prospects for therapeutic interventions are poor.[1-3] Celecoxib and sorafenib have shown some efficacy in retrospective studies, but the association of the two

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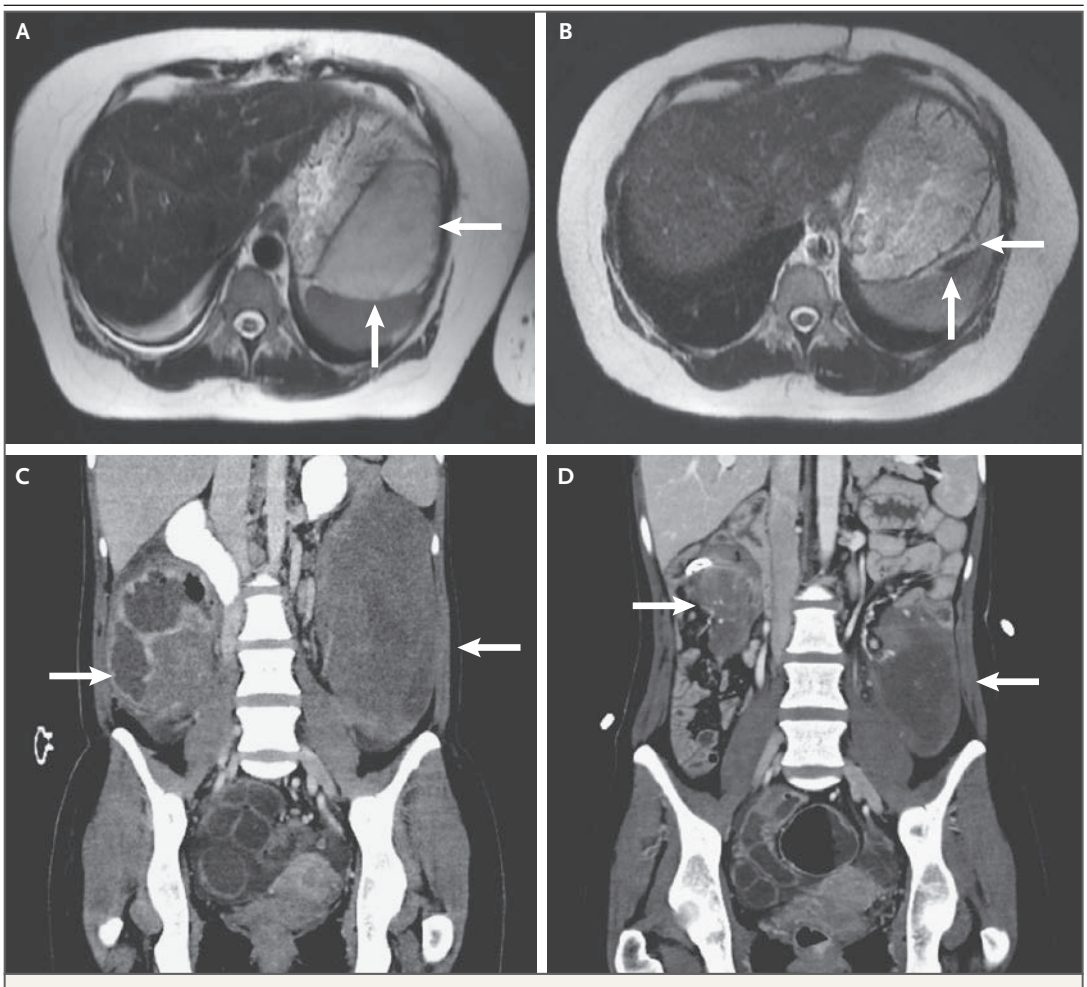

Figure 1. Imaging Studies from Two Patients with Familial Adenomatous Polyposis and Refractory Desmoid Tumors, before and during Combination Therapy with Celecoxib and Sorafenib.

Panel A shows the results of abdominal magnetic resonance imaging in Patient 1 before treatment with celecoxib and sorafenib, with arrows denoting a perigastric tumor. Panel B shows the results after 20 months of treatment, with arrows denoting the shrinkage of the tumor. Panel C shows the results of abdominal computed tomography in Patient 2 before the combination therapy, with arrows denoting a double-lobed desmoid tumor (arrows). Panel D shows the shrinkage of the tumor (arrows) after 6 months of treatment.

drugs has never been described.[4,5] The outcomes for these two patients provide potential equipoise for controlled studies of the celecoxib–sorafenib combination in patients with refractory desmoid disease associated with familial adenomatous polyposis.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Two-Year Outcome after Endovascular Treatment for Stroke

TO THE EDITOR: In their study of the 2-year outcome of endovascular treatment for ischemic stroke from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), van den Berg et al. (April 6 issue)[1] report a substantial delay (median, 101 minutes) between the initiation of alteplase and randomization. This finding suggests that perhaps at some sites clinicians may have waited to assess alteplase-induced recanalization before initiating endovascular treatment. Furthermore, the median time from stroke onset to groin puncture in the trial was as much as 263 minutes longer than the intervals reported in some other trials (e.g., Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial [EXTEND-IA], Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times [ESCAPE], and Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment [SWIFT PRIME]). In these three trials, patients proceeded to angiography as soon as possible, with times from stroke to groin puncture of 210 minutes, 200 minutes, and 224 minutes, respectively.[2]

Reducing delays in revascularization may increase the likelihood that endovascular therapy will be successful. Every 5-minute delay in the start of endovascular reperfusion has been estimated to worsen the clinical outcome for 1 in 100 patients.[3] Thus, delay could have reduced the effect of endovascular treatment in MR CLEAN as compared with EXTEND-IA, ESCAPE, and SWIFT PRIME.[2]

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THE AUTHORS REPLY: The main focus of our study was the long-term effect of endovascular treatment on clinical outcome in patients with acute ischemic stroke. Therefore, the median time from treatment with intravenous alteplase to randomization was not reported in the article published in the *Journal.* However, Zhang et al. are correct that in the original article from the MR CLEAN trial (published in the *Journal* in 2015[1]), the median time from onset to treatment was longer than in the trials that followed. However, the fact that the effect of endovascular treatment in the MR CLEAN trial was not as great as that in later trials cannot be attributed solely to this delay. This result is better explained by the trial's inclusion criteria, which were the widest and most pragmatic of all the studies of endovascular stroke. Current guidelines regarding patient eligibility for the endovascular treatment of stroke are therefore largely based on the results of the MR CLEAN trial.

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Since publication of their article, the authors report no further potential conflict of interest.

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