Letter to the Editor


We read with great interest the paper by Morimoto et al. (1) in the September 2002 issue of Clinical Cancer Research. We wish to share with the authors our experience from an unusual presentation of a glioblastoma multiforme grade IV. We witnessed peripheral angiogenesis inhibition, in the form of avascular necrosis at a distant skeletal site, as the first presenting complaint of a patient who was diagnosed shortly after as suffering from glioblastoma multiforme grade IV.

A 55-year-old woman presented with a 3-month history of bilateral ankle pain. There was no history of trauma or vascular disease, and she was on no medication over the past few years. Physical examination was unremarkable except for the ankle and hind foot, which had diffuse discomfort, but no signs of inflammation. All foot movements were within normal range. Hematology and serology for rheumatological and bone factors as well as plain radiographs were unremarkable. A 99Tc bone scan demonstrated focal areas of increased uptake in the tarsal bones bilaterally. Magnetic resonance imaging of the feet demonstrated bone edema in the right middle cuneiform and left navicular bones. Tissue microbiology after an aseptic biopsy under fluoroscopic control showed no organisms or crystals. Histopathology demonstrated thickened bony trabeculae with evidence of remodeling in the past, but the process appeared inactive. A diagnosis of bilateral avascular necrosis of the right middle cuneiform and left navicular bones was subsequently made because sepsis had been excluded, and this diagnosis fitted the clinical and radiological picture. The patient was treated conservatively with non-weight-bearing, below knee casts for 6 weeks. Six months later, she developed headaches with dizziness and needed urgent hospital admission after loss of consciousness with a Glasgow Coma Scale of 5. Computerized tomography demonstrated a heterogeneous lesion in the right frontal lobe with marked midline shift and contralateral ventricular dilation. The patient underwent a right frontal lobectomy, and a histopathological diagnosis of glioblastoma multiforme grade IV (WHO) was made. She received radical radiotherapy postoperatively but died 3 months later.

The pathogenesis of avascular necrosis of bone has been postulated to be mediated by cytokines acting as antiangiogenic factors, of which the most important ones are tumor necrosis factor α (2) and transforming growth factor β (TGF-β; Ref. 3). Several cytokines and their receptors have been identified as being important in the evolution of glioblastoma multiforme, but TGF-β has a pivotal role (4). TGF-β has an important physiological role in the brain of terminal glial cell proliferation in response to injury. TGF-β is a pleiotropic factor that has diverse effect on cell proliferation, differentiation, and matrix synthesis (5). It is a powerful autocrine growth inhibitor among normal glial cells, but it is a progression factor and a mitogen in glioblastoma and other central nervous system tumors (4). TGF-β is one of the most potent innate growth inhibitors and immunosuppressants known, but it is a powerful differentiation factor, too (4). TGF-β is generally well established as a growth inhibitor of endothelial cells (3). It has also been shown to activate coagulation and to inhibit fibrinolysis (6). The pathogenesis of avascular necrosis of bone has been attributed to the cytokines mentioned above. Indeed, the release of cytokines from tumors, which initiates a cascade of events that lead to vascular thrombosis, has been demonstrated repeatedly (2, 3). In particular, the role of TGF-β, which is critical in the development of glioblastoma and its associated antiangiogenic and prothrombotic effects, is a possible explanation for the pathology encountered in our case (7). The article by Morimoto et al. (1) has thrown more light on the antiangiogenic effect of malignant gliomas through the increased levels of tissue endostatin. However, our case possibly indicates that the effect of such an inhibitor may not only be local but systemic as well. We believe that the clinical case presented above will contribute to generating a hypothesis on the diverse effects of antiangiogenic factors released from glioma tumors. In conclusion, we agree that investigations on the regulation of endostatin mechanisms of action will facilitate the creation of effective antiangiogenic therapeutic approaches, but systemic effects of this approach should also be kept in mind.

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References


Reply

Tsiridis et al. presented an unusual case of avascular necrosis in the peripheral bone, which was later found to be combined with a glioblastoma in the brain. They suspected the avascular necrosis was caused by an endogenous inhibitor of angiogenesis, such as endostatin or transforming growth factor β, secreted from the glioblastoma tissue. Their hypothesis is very attractive. However, it is necessary to show data supporting a direct causal relationship between a glioblastoma and avascular necrosis of the peripheral bone. Detection of the tissue levels or serum levels of endostatin or transforming growth factor β could support the hypothesis. Although we showed increased levels of tissue endostatin in glioblastomas (1), we unfortunately did not examine the levels of endostatin in the serum for these patients. Furthermore, there have been no reports in which glioblastomas or other tumors secreting high levels of endostatin are combined with avascular necrosis of the peripheral bone (2, 3). With regard to the systemic effects of antiangiogenic therapies suggested by Tsiridis et al., no side effects such as avascular necrosis of the peripheral bone have been reported in a Phase I clinical trial of recombinant endostatin (4). However, this case report by Tsiridis et al. will promote further careful survey for the systemic effects of antiangiogenic factors in tumors secreting high levels of endostatin as well as in clinical application of recombinant endostatin.

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