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Letter to the Editor: Alveolar Soft Part Sarcoma With Lung Metastases. Response to Interferon Alpha-2a?

To the Editor: We read with interest the report by Pappo et al. entitled "Alveolar soft part sarcoma in children and adolescents: clinical features and outcome of 11 patients" [1]. Our experience with a boy with alveolar soft part sarcoma (ASPS) with lung metastases is relevant. The patient has remained in good health despite persistence of lung metastases over 9 years from the initial diagnosis and 6 years after discontinuation of chemo-cytokine therapy. Review of the course of his disease suggests a previously unknown susceptibility of ASPS to treatment with interferon alpha (INF-α).

A previously healthy 8-year-old boy presented without pain with an approximately 4-cm tumor on the upper and interior side of his left knee on 5 February 1991. The tumor was grossly resected and its histologic assessment led to a diagnosis of ASPS. Macroscopic findings at surgery indicated that the tumor was not well circumscribed and had invaded into the surrounding vastus medialis muscle. At the time of diagnosis, chest radiography and computed tomography (CT) scanning also revealed multiple pulmonary metastases. The patient was referred to the Kyoto Prefectural University of Medicine for postoperative chemotherapy. His treatment consisted of combinations of vincristine(VCR)/doxorubicin(ADR)/cyclophosphamide(CPM), etoposide/cisplastin, CPM/VCR/dactinomycin (Act-D), and ADR/VCR/ifosfamide. This was followed by maintenance therapy consisting of VCR, Act-D, and CPM for nine months between March 1991 and December 1991. The number and size of the lung metastases remained stable throughout the course of chemotherapy; after discontinuation of treatment, however, the lung metastases gradually grew in size and number. Consequently, in December 1992, the patient was treated with INF-α -2a (3 million IU, i.m. three times per week). After 6 months of interferon therapy (total doses 216 million IU), the number of lung metastases had decreased slightly, indicating a partial response (Fig. 1A). At this point, however, the patient and his parents refused to continue the treatment and the patient was lost to follow-up age eleven.

On 25 February 2000, at 17 years of age, the patient presented with chest pain to another hospital where multiple lung nodules were seen on chest X-ray films and CT scans. Given his past history of ASPS, he was referred to our hospital on 1 March 2000. We established there was no recurrence at the primary site and that the patient had been in good condition (Karnofsky score of 100%) during the intervening years without receiving any treatment. His complaint of chest pain was not related to the original disease. When the present and past lung CT scans were compared, we observed that his lung metastases had decreased in number and diameter. (Fig. 1B). His respiratory function was also found to be within normal limits (100.0% vital capacity, 104.3% forced expiratory volume$_{1.0}$). As the patient had a good quality of life, no organ dysfunction, and did not wish to be treated, we decided to withhold further therapy but to maintain close long-term surveillance.

Information on the precise long-term course to be expected in a case such as ours is limited. (2,3) Our survey of the literature revealed only three cases of ASPS with lung metastases surviving longer than 3 years at the time of those reports. These data must be coupled with the fact the nodules in our patient grew after chemotherapy and decreased in size only after the initiation of INF-α-2a. Spontaneous remission of disease seems a less likely explanation than ascribing the changes to INF-α-2a.

The possible efficacy of INF-α-2a in treating ASPS has not been previously reported, although experimental studies have shown that INF-α is effective in treating soft tissue sarcomas in general [4,5]. INF-α was found to inhibit their in vitro proliferation in a manner that is independent of their p53 status, although it did not induce apoptosis in a soft tissue sarcoma cell line [4]. In addition, Rosolen et al. [5] have shown that all solid tumors that develop during childhood express INF-α type 1 receptors and that treatment of these tumors with INF-α inhibits their in vitro growth. Given these data on the in vitro efficacy of INF-α, we speculate that the ASPS in our patient may have responded to and been stabilized by INF-α-2a, accounting for his long-term partial remission without disease exacerbation. It is thus of interest to know if ASPS expresses the INF-α receptor. Despite its characteristic histologic features, ASPS remains a tumor of controversial histogenesis and unclear pathogenesis. In the past, immunohistochemical studies have suggested that it may be both of neural and muscle

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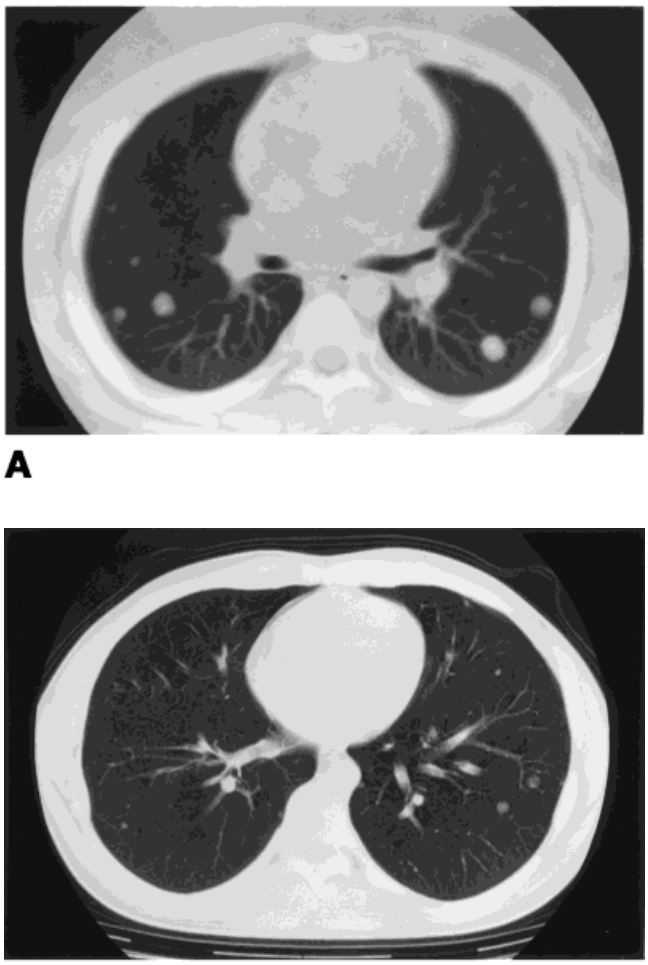

Fig. 1. Computed tomography of the patient's chest in March 1993 (A) and March 2000 (B).

origin [2,3], and recent reports have confirmed its neural origin by molecular and cytogenetic analyses [6]. Rosolen et al. [5] have shown that neuro-endocrine tumors that develop in childhood (i.e., neuroblastomas and primitive neuroectodermal tumors) express the INF-α receptor and are susceptible to the anti-proliferative effects of INF-α. Further studies are necessary to confirm the effectiveness of INF-α in treating ASPS and to assess how this might be related to the biologic characteristics and histogenesis of ASPS.

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