Interstitial Pneumonitis in a Patient with Melanoma Treated with the High Dose Interferon Alpha 2b Regimen

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The yearly increase in the incidence of malignant melanoma is among the highest of all human cancers. This year, 59,350 new cases are expected in the United States with 10,250 cancer-related deaths. High dose interferon alpha-2b regimen is currently the only regimen approved for adjuvant therapy in high risk melanoma patients. Here we describe a case of a melanoma patient who developed interstitial pnuemonitis as a complication of the high dose interferon alpha-2b regimen. Pneumonitis resolved following interferon withdrawal and a course of steroid therapy.

Patient Description

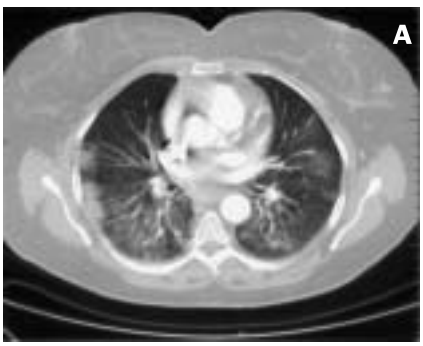
A 59 year old Caucasian female, who had been using steroids for the past 18 months to suppress symptoms of polymyalgia rheumatica, noted new changes in a long-standing right flank mole. Lesion biopsy, followed by wide excision resection and sentinel lymph node biopsy, revealed the diagnosis of malignant melanoma, Stage III-B, T4b, N2C, M0. The patient's prednisone was quickly tapered to 1 mg/day, and she was offered adjuvant therapy with the high dose interferon alpha-2b regimen. The intravenous part was relatively well tolerated. The subcutaneous dose, however, had to be reduced by 33% after the first week of therapy due to profound weakness, grade III hyponatremia and grade II myalgia. After 3.5 months from the start of the interferon regimen, the patient developed progressive shortness of breath and dry cough. On physical examination she was afebrile, her heart rate was regular at 88 with no abnormal heart sounds, and a few rales were heard over the lung bases. Her resting pulse-oximetry oxygen saturation was 95% at room air but dropped to 84% with ambulation. Chest X-ray showed increased bilateral interstitial markings. High resolution computed tomography images of the thorax revealed diffuse bilateral pulmonary interstitial and alveolar patchy infiltrates in a reticular pattern [Figure A]. CT angiography was negative for pulmonary embolus. The interferon was promptly discontinued and her steroids were increased to 40 mg of oral prednisone per day. The patient gradually decreased her prednisone dose for complete weaning within 8 weeks. A follow-up CT scan at 7 weeks revealed almost complete resolution of the pulmonary interstitial infiltrates with minimal residual opacities at the periphery of the lower lobes [Figure B].

Comment

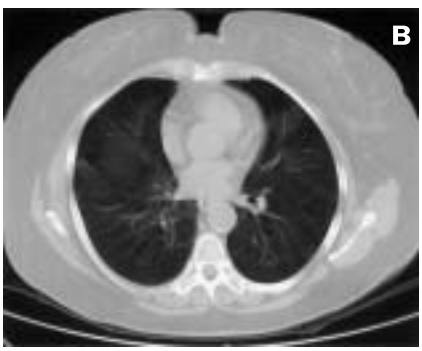
Interstitial pneumonitis, defined as diffuse parenchymal lung damage, is characterized by expansion of the interstitial component with infiltrates of inflammatory cells and accompanying fibrotic reaction. Clinically, patients present with progressive dyspnea and non-productive cough. Imaging studies with chest X-ray show diffuse interstitial opacities associated with reduced lung volume; high resolution CT scans show peripheral and bibasilar reticulonodular opacities associated with architectural distortion. In the appropriate clinical setting radiographic findings are sufficient to establish the diagnosis. Clinical conditions associated with an IP pattern include idiopathic pulmonary fibrosis, collagen vascular disease, drug toxicity, chronic hypersensitivity pneumonitis, asbestosis, and rare familial and genetic syndromes. Distinguishing the idiopathic forms from drug reaction is a matter of correlation with clinical information.

Rare instances of IP have been reported with interferon therapy in low dose regimens (3–5 million units/day subcutaneous 2–3 times weekly) in patients with hematologic malignancies, renal cell carcinoma

IP = interstitial pneumonitis



[A] High resolution CT scans of the chest demonstrating diffuse bilateral interstitial infiltrates in a reticular pattern and alveolar peripheral opacities.



[B] Follow-up CT scan of the chest 7 weeks after discontinuation of interferon therapy, demonstrating almost complete resolution of interstitial infiltrates with minimal residual opacities in the periphery of the lower lobes.

and hepatitis C infection [1–3]. Concomitant drug therapy with the antiviral nucleoside analogues zidovudine and ribavirin may have contributed to those cases, associated with T cell lymphoma and hepatitis C infection, respectively. High dose interferon alpha-2b regimen (intravenous induction phase with 20 million units/m^2/day for 20 days, followed by 10 million units/m^2/day subcutaneous 3 times weekly for 48 weeks) is currently the only regimen approved for adjuvant therapy in high risk melanoma patients. A review of toxicity data from three large randomized trials (Eastern Cooperative Oncology Group studies #1684, #1690, and #1694), that included 792 patients in the high dose interferon arms, did not disclose any report of grade 3 pulmonary toxicity in the form of IP [4]. Similarly, none were reported in 684 melanoma patients enrolling in studies with the low to moderate-dose interferon alpha 2a or 2b regimens. To the best of our knowledge, this is the first report of IP in a melanoma patient treated with the high dose interferon alpha-2b regimen.

Polymyalgia rheumatica is a rheumatic condition characterized by a subacute or chronic aching in the shoulders, hip girdles, neck and torso in patients aged 50 years or older. IP is not part of the PMR clinical spectrum, but it has been rarely reported in PMR patients exposed to HMG-CoA reductase agents [5]. Our patient had been taking the HMO-CoA-reductase inhibitor atorvastatin for the previous 5 years. This drug was not discontinued with the occurrence of IP and cannot be considered its cause. PMR is frequently associated with another rheumatic condition, giant cell (temporal) arteritis. Pulmonary involvement in the form of IP has been described in patients with GCA. PMR and GCA share immunologic defects in antigen selection and presentation and are both associated with the HLA-DR4 and a sequence polymorphism at the *HLA-DRB1* gene. Whether one develops PMR or GCA depends at least partially upon activated cytokines, with elevated levels of interleukin 2 associated with the former and high levels of interferon gamma and interleukin 1 with the latter. It is therefore possible that the immunologic abnormalities associated with the PMR diagnosis in our patient made her prone to develop IP in the presence of exposure to interferon.

In conclusion, physicians should be aware that IP may complicate high dose interferon alpha-2b therapy.

PMR = polymyalgia rheumatica
GCA = giant cell arteritis

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Reflex Sympathetic Dystrophy after Routine Venipuncture

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