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ORIGINAL ARTICLE

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Periostitis secondary to interleukin-11 (Oprelvekin, Neumega)

Treatment for thrombocytopenia in pediatric patients

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Abstract Interleukin-11 (Oprelvekin, Neumega) is a newly introduced thrombopoietic growth factor that stimulates production, differentiation, and maturation of megakaryocytes and platelets. Reversible periostitis has been reported as the side effect of the drug in primates and in the phase I/II trials. We report our experience with 5 cases of periostitis, occurring in thrombocytopenic children with three non-malignant and two malignant conditions, out of 24 pediatric patients treated with IL-11 at 75 μg/kg per day for a median of 17 days. The findings were noted in the clavicle or the proximal humerus. Two patients also had forearm and lower-extremity long-bone involvement. All patients had normal bones before IL-11 was given, changes occurred in both non-malignant and malignant diseases, and periostitis disappeared after use of the drug was discontinued. The distribution and appearance of the changes are similar to prostaglandin E1 and hypervitaminosis A. The changes are reversible after termination of treatment and are most noted in younger patients. The exact mechanism is not clear. The detection of periostitis makes it essential for the radiologists to enquire as to what medications patients are receiving. The pediatric doses (75 μg/kg/d) are above those recommended for adult patients (50 μg/kg/d) and this may account for the pediatric bone changes of periostitis.

Keywords Periostitis · Interleukin-11 · Neumega · Oprelvekin

Interleukin 11 (IL-11) Periostitis

Interleukin-11 (Oprelvekin, Neumega) is a thrombopoietic growth factor that stimulates production, differentiation, and maturation of megakaryocytes and platelets. It was introduced in adults to reduce the need for platelet transfusions and prevent severe thrombocytopenia following myelosuppressive chemotherapy in patients with non-myeloid malignancies whose disease and/or therapy has caused severe thrombocytopenia.

Recently, several phase I/II trials in pediatric patients confirmed its value as previously tested in adults [1, 2, 3]. Side effects common to adults and children included tachycardia, conjunctivitis, and cardiac arrhythmias. Papilledema occurred in children,although not in adults. Of interest was the observation of reversible periosteal new bone formation, which occurred in 10% of children in these trials [3]. It did not seem to affect growth plates or cause pain. (The manufacturer's data confirm these periosteal changes to occur in non-human primates as well) [4]. Tendon fibrosis and capsule fibrosis also occurred.

We report our experience, in 2000-2001 with 5 cases developing periostitis out of 24 pediatric patients treated with IL-11. The patient population included not only malignancies, but also patients with non-malignant diseases (thalassemia, erythrophagocytic lymphohistiocytosis, Fanconi's anemia, Wiskott-Aldrich syndrome).

The changes occurred after several weeks of IL-11 therapy and slowly disappeared after the drug was stopped.

Materials and methods

A retrospective case series review was performed. The following patient population was studied: all pediatric patients aged 5 months to 18 years of age, receiving IL-11, in the period of August 2000 to December 2001. The list of pediatric patients was obtained from the oncology pharmacy staff. All patients had doses of 75 μg/kg per day for a median of 17 days. The ages ranged from 5 months to 18 years. The patients had a variety of diseases, ranging from non-malignant genetic and immune disorders such as Wiskott-Aldrich syndrome (2), thalassemia (1), erythrophagocytic lymphohistiocytosis (1), Fanconi's anemia (2) to malignant diseases such as Wilms' tumor (2), neuroblastoma (2), Hodgkin's lymphoma (3), non-Hodgkin's lymphoma (2), leukemia [ALL (5), AML (2), and CML (2)]. Most of these patients had cord stem-cell transplantation.

All available films were reviewed from the CR-PACS system on the patients, the majority of whom were either in the ICU or hospitalized on the transplant service owing to their extreme immunosuppressed status. Films were virtually always chest films or chest/abdomen, as the patients continuously had fever, hypoxic episodes, and abdominal pain. Formal skeletal surveys were not done.

Results

All films on the 24 patients receiving IL-11 were reviewed by three observers. Five of 24 patients in the study period developed recognizable periostitis on chest radiographs. The observed periostitis was sometimes limited to a single line and sometimes laminated. The findings were noted in the clavicle (Fig. 1) or the proximal humerus (Fig. 2). In each case, since most patients had virtually daily films, the initial changes were not recognized until they reached either a particular size or the area—such as the humeral shaft—was well covered. All five had humeral changes and two had clavicle laminated new bone. Over time, after discontinuation of the IL-11, the changes were absorbed into the involved bones. Two patients (one with neuroblastoma and one with Wiskott-Aldrich syndrome) had other sites: forearm and lower extremities. One of the patients with neuroblastoma had a bone scan demostrating increased radiotracer uptake in the forearm (Fig. 3). There was some subjective discomfort in the Wiskott-Aldrich patient. It was beyond the scope of this study to correlate the findings with either clinical or laboratory changes.

Discussion

We believe that periostitis observed in patients receiving IL-11 (Oprelvekin, Neumega) is secondary to the drug because of the following reasons:

1. All patients had normal bones before the drug was given.
2. The changes occurred in patients with both non-malignant and malignant diseases.
3. The bone changes disappeared after use of the drug was discontinued. (The two patients with neuroblastoma had no evidence of metastatic lesions or bone marrow involvement during or after the drug administration.)

The distribution of changes—clavicles and long bones—is similar to changes observed in infants receiving prostaglandin E1 therapy to maintain ductus

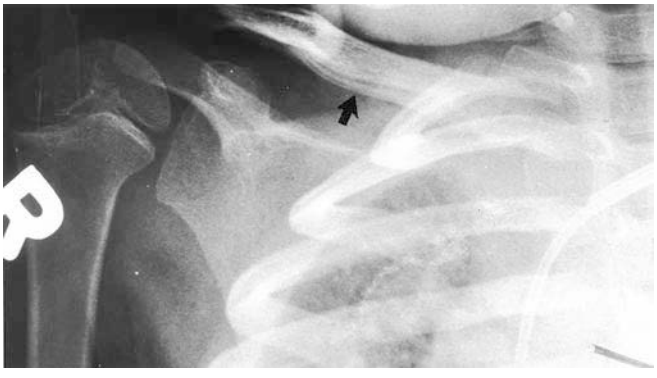

Fig. 1 Extensive laminated periostitis in the undersurface of the right clavicle. Similar changes were noted in the left clavicle, bilateral humeri, and femoral shafts in this 15-month-old patient, who at this time was in a disease-free state of neuroblastoma

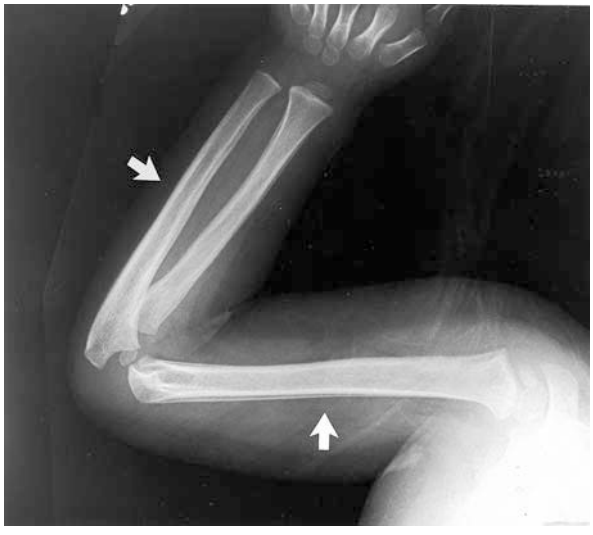

Fig. 2 Right and left humerus, ulnar and radius demonstrate smooth laminated periostitis in this 3-month-old patient with Wiskott-Aldrich syndrome. This was one of the two affected siblings

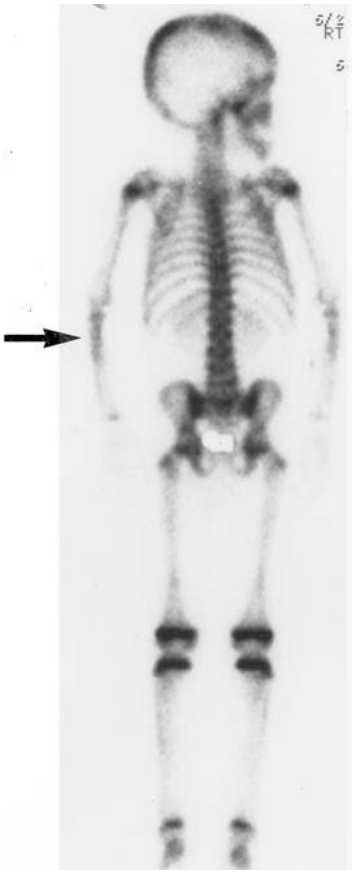

Fig. 3 Increased uptake in the proximal half of the forearm bilaterally, corresponding to periostitis seen of the radiograph. This is a 2 1/2-year-old child, who at this time was in a disease-free state of neuroblastoma, following cord stem cell transplant

arteriosus patency. There is also some similarity to the changes and sites seen in hypervitaminosis A. Of note, periostitis, in patients taking vitamin A only occurs as a sign of toxicity. Our patients received therapeutic doses of IL-11, not toxic. None of the patients was receiving prostaglandin therapy, and none was receiving vitamin A treatment or its analogs (*cis* retinoic acid). The patients were often receiving GMCSF and/or GCSF (granulocyte macrophage colony stimulating factor); however, these drugs do not cause periostitis in clinical or animal work. The affected patients were part of a larger group of patients receiving IL-11 treatment to reduce the need for platelet transfusions for the severe thrombocytopenia that had resulted from their chemotherapy or cord stem-cell transplant. The pediatric doses (75 μg/kg/d) are above those recommended for adult patients (50 μg/kg/d) and this may account for the pediatric bone changes of periostitis.

Finally, there is a slight resemblance to hypertrophic pulmonary osteoarthropathy, but none of the patients had chronic suppurative lung disease.

In conclusion, IL-11 is a ''new cause'' of periostitis in long bones and clavicles, as noted on chest films in patients with both non-malignant and malignant diseases. The common denominator is the drug, not the primary disease. The exact mechanism is not clear. The changes were most noted in the younger patients. IL-11 (Neumega) therapy has to be added to the list of drug-related periostitis (vitamin A poisoning, prostaglandin E-1 therapy). Radiologists seeing such findings have to inquire as to what medications patients are receiving.

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