Neuroblastoma, an embryonal malignant tumor of the sympathetic nervous system, is the most common solid tumor in the first years of life. It has a very poor prognosis if metastatic disease is diagnosed after 1 year of age.1 High-dose chemotherapy/radiotherapy followed by autologous bone marrow transplantation can improve the chance of disease-free survival, but the relapse rate remains high.2

Radiolabeled metaiodobenzylguanidine (MIBG) is accumulated in neuroblastoma cells.3 Scintigraphic examination with MIBG labeled with iodine ([123I]MIBG) is used for assessing the extent of the neuroblastoma and is suitable for diagnosis and staging as well as follow-up.4 Because of its high concentration in neuroblastoma lesions and its β(electron)-emission capacity, use of [131I]MIBG is a new therapeutic approach in the disease, especially in its disseminated form.5 Normally, MIBG is also accumulated in the salivary glands.6-8 The side effects of [131I]MIBG treatment are nausea, vomiting, and hematologic effects, particularly thrombocytopenia and neutropenia.2,9

In this report, severe oral mucositis induced by [131I]MIBG treatment in a girl with stage 4 neuroblastoma is described.

**Objective.** The purpose of this report is to document a newly encountered oral side effect of targeted radiotherapy with iodine 131–metaiodobenzylguanidine ([131I]MIBG) in the treatment of neuroblastoma.

**Study design.** A 14-month-old girl was diagnosed with stage 4 neuroblastoma. After completion of chemotherapy, the tumor showed no signs of regression; treatment with 3700 MBq [131I]MIBG was therefore decided on, 8 months after diagnosis.

**Results.** Fourteen days after infusion of MIBG, severe oral mucositis was diagnosed, with a generalized erythema involving the mucous membranes of the hard and soft palate, buccal mucosa, and upper and lower lips. The gingiva exhibited a general linear erythema.

**Conclusions.** Visualization of the salivary glands on [123I]MIBG images suggests that accumulation of radiolabeled MIBG in the salivary glands may be related to sympathetic innervation.

Oral mucositis

Seven days after [131I]MIBG therapy, the child showed signs of oral discomfort, with an increasing erythema of the mucous membranes. Fourteen days after the infusion, severe oral mucositis was diagnosed. A generalized erythema involving the mucous membranes of the hard and soft palate, buccal mucosa, and upper and lower lips was found. The gingival tissues were not affected, except for the free gingival margin surrounding the erupted primary teeth, which exhibited a general linear gingival erythema (Fig 2). The dorsal tongue exhibited a pseudomembranous lesion. Signs of oral dryness were also evident. Cultures of the oral cavity, throat, and nasopharynx yielded no positive bacterial or fungal growth.

The period of oral mucositis, oral discomfort, and erythema of the palate, lips, and tongue persisted for more than 5 weeks after start of [131I]MIBG treatment. The oral erythema gradually subsided, whereas the linear gingival erythema persisted despite oral hygiene measurements. During this period no evidence of primary or secondary herpes virus infection could be identified by means of blood cultures.

One month after the [131I]MIBG treatment, there was a new period of suspected septicemia. Two months after the MIBG treatment (ie, almost 9 months after diagnosis), the child died as a result of progressive disease in respiratory insufficiency.

DISCUSSION

Radiolabeled MIBG was originally developed for the imaging of diseases of the adrenal medulla, but it also depicts neuroblastomas and various neural crest tumors. MIBG acts as an analog of the neurotransmitter and hormone norepinephrine (NE). MIBG shares many cellular transport properties with NE, such as entry into adrenergic cells via a particular uptake pathway, storage in vesicles, and secretion in response to acetylcholine.

Treatment with [131I]MIBG is generally well tolerated; however, there are some specific side effects. The degree of thrombocytopenia and neutropenia is correlated with the absorbed whole body dose and is due to specific uptake in the megakaryocytes and to bone marrow depression—the latter in particular when treatment is preceded by chemotherapy, according to Lashford et al. Primary hypothyroidism occurs frequently after [131I]MIBG administration despite iodide administration to block the thyroid uptake of [131I]MIBG. Other reactions include nausea, vomiting, chest pain, pyrexia, and a hepatic, and possibly a renal, effect. In a study by Garaventa et al, oral mucositis was registered in one child and moderate sialadenitis for a few days was noted in another; however, no comments were made concerning the etiology.

Prominent among the tissues regularly visualized on scintigraphic images made with MIBG are the salivary glands, particularly the parotid gland; this is because...
salivary glands are richly innervated by adrenergic nerves. In addition to the salivary glands, the heart, liver, spleen, and urinary bladder are regularly depicted at examination. In diagnostic [123I]MIBG, the salivary glands are visualized in 92% to 100% of patients, as reported by Nakajo et al. Accumulation of [131I]MIBG in the salivary glands may be related to sympathetic innervation, inasmuch as the glands are richly supplied with sympathetic nerve fibers. The uptake of iodine labeled MIBG mimics, in part, that of NE, but a considerable amount of the salivary MIBG resides in extraneuronal sites. Sisson et al suggested that MIBG enters or is adherent to parenchymal cells of the salivary glands but does not find its way to the secretory system. It is therefore plausible that there is uptake of [131I]MIBG in the salivary glands distributed in the oral cavity, which would have contributed to the mucositis seen in this case.

The clearance of [131I]MIBG from plasma is very rapid; in our patient, the saliva-to-plasma ratio of the radioactivity was greater than 1.0 from 15 minutes to 48 hours after [131I]MIBG injection. Most of the radioactivity in the saliva is in the form of free 131I ions. The presence of radioactive saliva in the mouth may also superimpose physiologic areas of uptake and bone, increasing the risk of diagnostic errors. This may also contribute to the dose to the oral mucous membranes.

Mucositis is a common side effect of chemotherapy and radiotherapy. In this case, chemotherapy-induced mucositis can be ruled out because the last treatment was completed 6 weeks before [131I]MIBG therapy was started. Oral infection with Candida albicans can give rise to oral erythema similar to that seen in our patient, especially in immunocompromised individuals. In this case, however, no evidence of fungal infection could be verified by means of cultures from the blood and oral cavity. Linear gingival erythema, seen in the marginal gingiva in our patient, has been reported in immunocompromised children with AIDS and in children with Down’s syndrome. Furthermore, primary infection with herpes simplex virus may induce symptoms similar to those seen in this child, but we could find no evidence of primary or secondary herpes virus infection.

Healing of the oral lesion was slow in our patient, which can be explained by the slow recovery after [131I]MIBG therapy. In a study by Hutchinson et al, the absolute neutrophil count nadir was found to occur at a median of 40 days (range, 20-52 days) after the initial [131I]MIBG therapy. In bone marrow transplant patients, it has been shown that healing of oral lesions coincides with establishment of the new marrow and increases in white blood cell counts and thrombocyte

oral mucositis may thus be overlooked as a side effect in the treatment of children with neuroblastoma who are treated with [131I]MIBG.

In conclusion, this is the first report of the development of severe oral mucositis after [131I]MIBG therapy in a child with neuroblastoma; it suggests specific uptake by sympathetic neuronal elements.

REFERENCES
15. Picco P, Garaventa A, Claudiani F, Gattorno M, De Bernardi B. Bone, increasing the risk of diagnostic errors. In conclusion, this is the first report of the development of severe oral mucositis after [131I]MIBG therapy in a child with neuroblastoma; it suggests specific uptake by sympathetic neuronal elements.

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