Peptide Receptor Radionuclide Therapy for Sarcoidosis

To the Editor:

A 46-year-old woman with drug-resistant multiorgan sarcoidosis was referred for further workup. The initial diagnosis of sarcoidosis had been established in 2010 when recurrent courses of uveitis raised the concern for a systemic immune-mediated disease and computed tomography (CT) revealed bihilar lymphadenopathy, multiple lung nodules, and splenomegaly. The presence of noncaseating granulomas highly consistent with sarcoidosis was confirmed by mediastinal lymph node biopsy. Therapy with high-dose prednisone (100 mg/d) was initiated but was terminated after 3 months because of persistent inflammatory activity and new-onset diabetes. In addition, the patient perceived growing bone pain due to osseous involvement as confirmed by fluorodeoxyglucose–positron emission tomography (PET)/CT and repetitive biopsy. Methotrexate (25 mg/wk) and dipyrone were prescribed but had no benefit. In the following years, the patient experienced ever increasing pain and was administered various drug regimens, including etanercept (50 mg once weekly), methotrexate (15 mg once weekly) plus adalimumab (40 mg once weekly), cyclophosphamide, and azathioprine, all without any effect on inflammatory activity or relief in symptoms. By mid-2014, the patient had exhausted all conventional treatment options; prescribed symptomatic medication consisted of a combination of oxycodone (80 mg every 8 h), etoricoxib (90 mg once daily), and carbamazepine (150 mg twice daily). However, she still experienced debilitating bone pain. Evaluation at our sarcoidosis center prompted the idea of somatostatin receptor (SSTR)–directed peptide receptor radionuclide therapy (PRRT).

The clinical ethics committee of our institution (Universitätsklinikum Würzburg) approved the individual treatment on a compassionate use base (German Drug Act, §13,2b). The patient gave written informed consent before therapy.

Because pretherapeutic SSTR-PET/CT (Siemens Biograph mCT 64, Siemens, Knoxville, TN) with ^{68}Ga-DOTA(0)-D-Phe(1)-Tyr(3)-octreotide (DOTATOC) demonstrated enhanced tracer accumulation in mediastinal lymph nodes and throughout the skeleton, consistent with multiple active granulomas, SSTR-directed PRRT appeared feasible. However, the disseminated pattern of bone marrow involvement raised the concern for extensive hematological effects of radionuclide-based therapy.

Table 1. Laboratory Data

	Reference Range, Adults	Before PRRT	3 wk after PRRT	6 wk after PRRT	10 wk after PRRT
Hematocrit,%	35–47	34.0	32.7	34.9	32.5
Hb, g/dl	12–16	11.2	10.0	11.2	10.7
White-cell count, per mm^3	4,500–11,000	5,800	3,400	2,700	3,400
Absolute neutrophil count, per mm^3	1,200–7,200	4,940	2,768	2,244	n/a
Differential count, %					
Neutrophils	41–70	84.5	81.4	83.1	n/a
Lymphocytes	23–40	9.8	7.4	8.3	n/a
Monocytes	2–8	3.4	8.3	5.6	n/a
Eosinophils	0.8–6.2	2.1	2.9	3.0	n/a
Basophils	0–1	0.2	0	0	n/a
Platelet count, per mm^3	150,000–450,000	221,000	221,000	169,000	186,000
Prothrombin time, s	11.0–14.0	13.7	14	n/a	14
Prothrombin time international normalized ratio	0.85–1.18	1.11	1.02	n/a	1.02
Activated partial-thromboplastin time, s	23–36	30.7	26.9	n/a	26.9
Sodium, mmol/L	135–145	138	137	141	141
Potassium, mmol/L	3.5–5.0	4.4	4.8	4.6	3.7
Calcium, mmol/L	2.0–2.7	2.2	2.2	2.2	2.1
Chloride, mmol/L	94–110	98	100	104	101
Creatinine, mg/dl	0.0–0.95	0.79	0.88	0.75	0.89
Estimated glomerular filtration rate, ml/min/ 1.73 m^2; CKD-EPI		90	79	96	78
Urea nitrogen, mg/dl	10–50	20.4	19.9	22.8	17.8
Uric acid, mg/dl	2.4–5.7	4.6	3.7	4.6	6.4
Cholinesterase, U/L	5,320–12,920	8,755	6,271	7,493	8,082
Total bilirubin, mg/dl	0.1–1.2	1.0	0.4	0.5	0.5
Aspartate aminotransferase, U/L	⩽35	87.4	25.0	28.0	24.0
Alanine aminotransferase, U/L	⩽35	21.9	16.0	20.0	18.0
γ-Glutamyltransferase, U/L	⩽40	28.1	32.1	29.3	43.2
Alkaline phosphatase, U/L	35–105	104	119	165	132
Amylase, U/L	⩽110	40	57	38	27
Lipase, U/L	13–60	15	18	20	12
Soluble IL-2 receptor, U/ml	⩽900	1968	n/a	n/a	1,021

Definition of abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration; n/a = not available; PRRT = peptide receptor radionuclide therapy.

Because of the unprecedented experimental setting in this special patient, harvest of peripheral blood progenitor cells as backup in case of severe hematotoxicity was considered mandatory. Mobilization of stem cells by priming with granulocyte colony-stimulating factor under close surveillance was attempted but did not result in an adequate cell dose. In addition, the patient complained about increasing abdominal pain that was caused by growing splenomegaly, thereby preventing prolonged or intensified stimulation. Instead, bone marrow harvest from the posterior iliac crests under general anesthesia was successfully executed. PRRT was performed according to the joint International Atomic Energy Agency, European Association of Nuclear Medicine, and Society of Nuclear Medicine and Metabolic Imaging practical guidance with 8.4 GBq of ^{177}Lu-DOTATOC intravenously administered over 30 minutes (1). Vital signs were documented every 5 minutes during and twice daily after treatment administration (for 7 d). Standard serum parameters and complete blood counts (including differential counts) were recorded before and every week after PRRT.

Post-therapeutic γ-camera whole-body imaging was performed at 2, 24, and 72 hours after injection of the radiopharmaceutical. At 24 hours, additional tomographic single-photon emission CT in combination with low-dose CT of the abdomen and pelvis was performed. All images were acquired using dual-head γ-cameras (Siemens Symbia E for planar imaging, Siemens Symbia T2; Siemens, Erlangen, Germany) equipped with medium energy collimators. The absorbed doses in tumors and organs were assessed by analyzing regions of interest. Pharmacokinetic data were fitted by biexponential functions.

PRRT was well tolerated without any acute adverse effects. No changes in vital signs were recorded. Post-therapeutic scintigraphic imaging demonstrated ^{177}Lu-DOTATOC uptake in all osseous and mediastinal granulomatous lesions, consistent with pretherapeutic PET/CT imaging. Absorbed lesion doses were estimated to reach up to 10 Gy (in mediastinal lymph nodes). In the subsequent weeks, apart from transient slight leukopenia, repeated blood tests remained unremarkable; no changes in kidney function were observed (Table 1). Three weeks after treatment, the patient noticed ameliorated pain with a pronounced reduction during rest. At first restaging after 6 weeks, pain during rest had completely resolved, for the first time since the initial diagnosis. On SSTR-PET/CT, treatment response was visualized by significantly decreased tracer accumulation in all osseous lesions, as well as mediastinal lymphadenopathy, the latter of which also demonstrated a morphological response (Figure 1). A drop in soluble IL-2 receptor levels was recorded. In addition, pulmonary function tests, complete blood counts, and chemistry were unremarkable, thereby alleviating the concern for relevant bone marrow depression. Because of the good tolerability of the treatment, a subsequent therapy cycle to further suppress persistent inflammatory activity was performed when bone pain mildly recurred (12 wk after first cycle). Of note, this second cycle was also excellently tolerated and resulted in a new pronounced relief of pain, which is still ongoing (6 mo after the initial treatment).

Osseous involvement in sarcoidosis occurs in less than 5% of patients (2, 3). Although most patients are asymptomatic, sarcoid bone involvement indicates a chronic and more severe course of the disease (4). Our patient experienced diffuse skeletal involvement that resulted in debilitating bone pain refractory to all conventional therapeutic agents. Because activated macrophages have been shown to overexpress SSTR II on their cellular surface, which can be visualized by receptor-directed imaging (5–9), we hypothesized that active sarcoid granulomas might be effectively targeted by endoradiotherapy using a radiolabeled SSTR-ligand. General target expression was proven by ^{68}Ga-DOTATOC-PET/CT. Because of the high level of patient distress and the lack of treatment alternatives, we decided to perform PRRT. Although the treatment is well-established in patients with neuroendocrine tumors and generally well tolerated (10), we opted for stem cell support to be able to counteract a potential depression of hematopoiesis, because of the diffuse bone marrow involvement in our patient. Therapy with a standard activity of ^{177}Lu was well tolerated, and laboratory tests provided no evidence of major effects of PRRT on either bone marrow or kidney function. Although

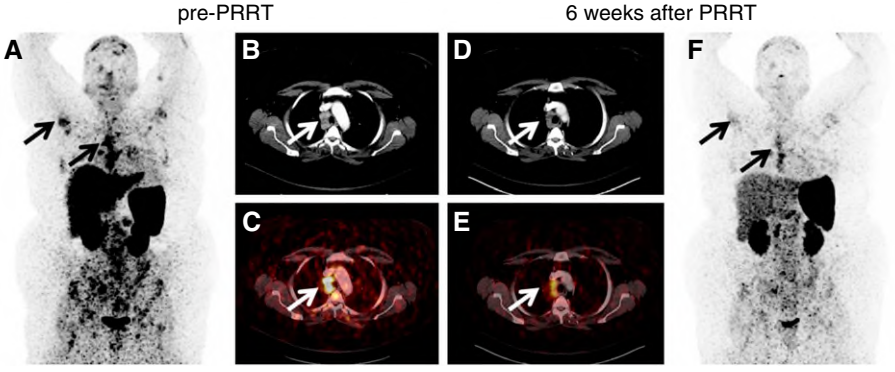

Figure 1. Display of somatostatin receptor–directed positron emission tomography (PET) with ^{68}Ga-DOTA(0)-D-Phe(1)-Tyr(3)-octreotide before and 6 weeks after peptide receptor radionuclide therapy (PRRT) with ^{177}Lu. Display of maximum intensity projections (*A* and *F*) and transaxial slices of computed tomography (CT) (*B* and *D*) and fused PET/CT (*C* and *E*) images before (*A–C*) and 6 weeks after (*D–F*) somatostatin receptor–directed PRRT. PRRT resulted in symptomatic relief, as well as a partial morphologic and metabolic response. Both PET projections are displayed with the same intensity. *Black arrows* in *A* and *F* depict osseous lesions in the sternum as well as right humerus. *White arrows* in *B–E* show mediastinal lymph nodes.

absorbed granuloma doses can be assumed to be rather modest, both a subjective and an objective treatment response were achieved. This case is the first description of successful therapeutic targeting of somatostatin receptors in inflammatory diseases. We conclude that PRRT might be a new valuable tool in patients with otherwise treatment-refractory sarcoidosis. Further evaluation of this treatment option is warranted. ■

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Early Elevation of Plasma Periostin Is Associated with Chronic Ventilator-Dependent Bronchopulmonary Dysplasia

To the Editor:

Bronchopulmonary dysplasia (BPD), an inflammatory chronic lung disease of extreme prematurity, affects 12,000 infants annually and contributes significantly to immediate and lifelong morbidity. Although several serum biomarkers have been associated with the need for supplemental oxygen or respiratory support at 36 weeks postmenstrual age (PMA) (1), biomarkers are needed to identify infants who will develop the most severe form of BPD, which requires tracheostomy and chronic home ventilation. Infants requiring chronic home ventilation are particularly vulnerable to poor respiratory outcomes (2) and may derive the most benefit from early, directed anti-inflammatory therapy (3). The matricellular protein, periostin, increases in response to airway epithelial injury and has been implicated in immunomodulation, mucous production, and extracellular matrix remodeling associated with asthma and pulmonary fibrosis (4). In severe adult asthma, greater responsiveness to anti–IL-13 therapy was predicted at the time of enrollment by elevated plasma periostin (5). In adults and children with asthma, elevated plasma periostin correlates with greater airflow limitation, airway hyperreactivity, decline in pulmonary function, and disease severity (6–8). In autopsied lungs of extremely preterm infants who died with severe BPD, periostin expression is increased (9, 10), but the ability of circulating periostin levels to predict chronic ventilator-dependent BPD has not been established. Therefore, we sought to define the relationship between circulating periostin levels in extremely preterm infants in the first postnatal weeks and the development of severe, chronic ventilator-dependent BPD. Some of the results of these studies have been previously reported in the form of an abstract (11).

Infants enrolled in the Prematurity and Respiratory Outcomes Program (PROP) study (12) at Indiana University between October 2013 and January 2015 were eligible for this substudy if, at 7 days of age, they required any respiratory support more than 2 L/min nasal cannula or positive pressure ventilation. Plasma periostin at 7 and 28 days of age was analyzed via multiplex immunoassay. BPD status was determined based on the physiological need for supplemental oxygen at 36 weeks PMA (12). Chronic ventilator-dependent BPD was defined as the need for tracheostomy and mechanical ventilation at discharge.

Of the 31 infants enrolled, 15 (48%) were diagnosed with BPD and 5 (16%) died before classification. As expected, infants that died or developed BPD were of lower gestational age, had higher rates of

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