Polymyalgia rheumatica in a melanoma patient due to nivolumab treatment

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Editor,

A 75-year-old man complained of generalized joint pain. He had undergone total resection of malignant melanoma in the left lumbar region seven years previously. One year previously, computed tomography

(CT) showed left pelvic lymph node metastasis (cT3N1bM1a, stage IV), and immunotherapy with nivolumab was started. Nivolumab was started at a dose of 3 mg/kg, and a total of three courses were administered. Approximately two months after the start of treatment, generalized pain appeared, and after approximately three months, morning stiffness was making ADL so difficult for the patient that he was obliged to stay in bed until midday. Muscle weakness of the arms and legs was present, predominantly affecting the proximal muscles, and restricted joint range of motion and pain on movement were also present. Serological tests showed that, although neither creatinine kinase nor aldolase was elevated, C-reactive protein (8.77 mg/dl) and erythrocyte sedimentation rate (75 mm/h) were both high. Rheumatoid factor (RF) and autoantibodies, such as anti-citrullinated protein antibody (CCP), were negative. Shoulder joint ultrasonography showed tenosynovitis of both biceps brachii. Gallium-67 scintigraphy showed uptake in the arm and leg joints, suggesting systemic arthritis (Figure 1). Vascular ultrasound of the temporal artery showed no thickening of the vascular walls, ruling out giant-cell arteritis.

The diagnostic criteria for PMR include age ≥50 years, pain in both shoulders, and elevated ESR and CRP as essential conditions. All these were met in the present case. In addition to these essential conditions, a definitive diagnosis of PMR is reached on the basis of a score of ≥5 points on screening

using arthritis symptoms and joint ultrasonography findings. The present patient scored 6 points (morning stiffness, pain and limited range of motion in the gluteal region, negative for RF and anti-CCP antibodies, and signs of bursitis on bilateral shoulder joint ultrasonography), and a definitive diagnosis of PMR associated with nivolumab treatment was reached (Bird et al. 1979; Dasgupta et al. 2012). Nivolumab was discontinued and oral prednisolone 20 mg/day was started to treat the PMR without giant-cell arteritis. Within 24 hours of the start of treatment, the joint pain had greatly improved, and after three weeks, the morning stiffness and difficulty walking had resolved, and the patient's ADL had improved.

Nivolumab is an anti-programmed cell death 1 (PD-1) antibody that has been attracting attention as a checkpoint inhibitor, and it has recently come into use as an effective antineoplastic agent for metastatic tumor such as malignant melanoma (Larkin et al. 2015). Although its known side effects include autoimmune diseases such as myasthenia gravis, polymyositis and Guillain–Barré syndrome (Kimura et al. 2016; Jacob et al. 2016), no previous case of PMR as a result of nivolumab administration has been reported. When the binding between PD-1 and its ligand is blocked by nivolumab, the induction of immunosuppressive T cells is blocked, and the inhibition of the cancer antigen-specific T-cell response is suppressed (Wang et al. 2014). This acts to inhibit tumor growth, but it is also believed to cause an abnormal T-cell response. Such an abnormal immune response is implicated in the development of PMR.

This is an important case demonstrating that PMR, an autoimmune disease, may occur as a side effect of nivolumab.

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Compliance with ethical standards

Conflict of interest: All authors declare no conflicts of interests.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: Informed consent was obtained from an individual participant included in the case.

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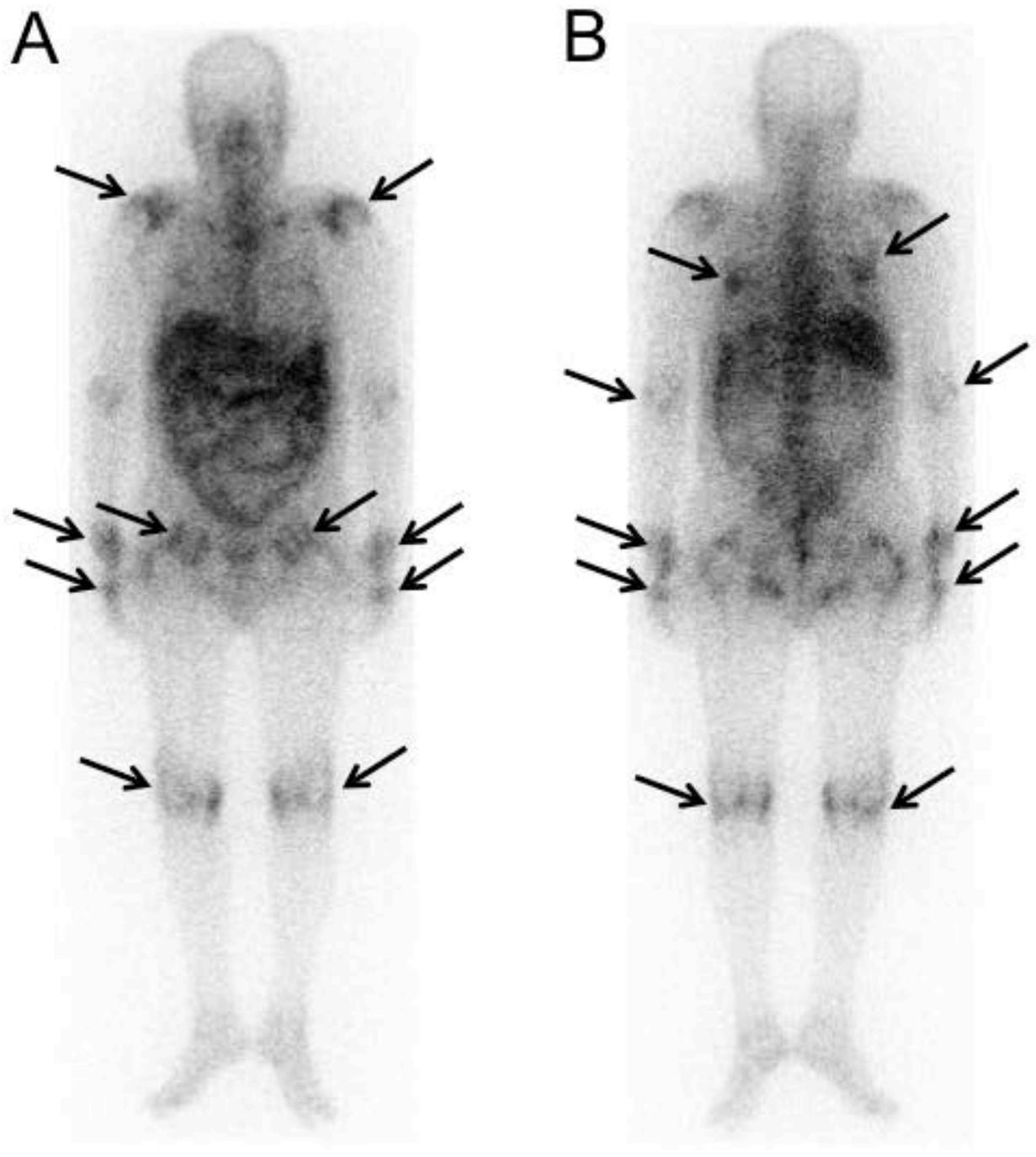
Figure legend

Figure 1: Gallium-67 scintigraphy

Bilaterally symmetrical areas of uptake are evident mainly in the shoulders and hips, with some uptake also in the elbows, wrists, knees, and the inferior tip of the scapula (arrows). These findings are suggestive of systemic arthritis. Figure 1A shows an anterior view, and Figure 1B a posterior view.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