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## TITLE

**Unconventional immune-related phenomena observed using 18F-FDG PET/CT in Hodgkin Lymphoma treated with anti PD-1 monoclonal antibodies**

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## KEYWORDS

Nivolumab; pembrolizumab; anti PD-1; 18F-FDG PET; PET/CT; computed tomography; Hodgkin lymphoma.

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**CONFLICT OF INTEREST**

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## TEXT

The paradigm of response in Hodgkin lymphoma (HL) was developed in cytotoxic chemotherapies and its use as a reference model for immune-modulatory regimens, which restores the immune system's anti-tumor capacity, is questioned [1, 2]. In a centralized review, we retrospectively analyzed 60 consecutive patients from 34 participating institutions with relapsed or refractory (R/R) HL treated with nivolumab after institutional review board approval. We observed unconventional immune-related phenomena regarding tumor response or progression, and adverse events (irAE). Transient progression in lesions size and metabolism, while the patients were continuing Nivolumab, were observed in 3.3% of patients at 3 months (**A, B**). Nonetheless, while pseudo-progression represents the most described immune-related pattern of response in solid tumors, along with abscopal effect and hyperprogression [3, 4], these early pseudo-progressive lesions did not significantly alter response evaluation since they were all observed in unequivocally progressive patients. The most significant encountered problems were mixed responses (**B**) and irAEs (**A, C**). Medical imaging detects 74% of irAE [5] in solid tumors, which can occur theoretically at any site and at any time. The most frequent sites reported in solid tumors are lung, mediastinal lymph nodes (sarcoidosis-like), enterocolitis, hypophysitis, thyroiditis, hepatitis, arthritis, and pancreatitis. While we identified such irAE in our cohort, we also identified imaging findings suggestive of gastritis and hemolytic anemia (**A, C**). In clinical routine, these immune-related phenomena should be considered as potential differential diagnoses (e.g., an increased spleen metabolism can be observed in true progression, spleen activation reflecting treatment efficacy [4], and irAE).

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