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Letter to the Editor

A Rare Immune-Related Mesenteric and retroperitoneal serositis in a Multi-Refractory Hodgkin Lymphoma Patient Successfully Treated with Chylolymphostatic Surgery

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To the editor.

Hodgkin lymphoma (HL) is a rare hematological malignancy localized to lymph nodes, where neoplastic cells, also termed Reed-Sternberg and Hodgkin cells, are surrounded by mature non-neoplastic inflammatory cells and diffuse collagen fibrosis. Classic HL (cHL) is largely treatable with conventional chemotherapy, with an estimated 5-year survival of approximately 88%.[1] In advanced disease, frontline therapy has changed over the years, as patients are currently treated with ABVD or BV-AVD regimen (brentuximab-vedotin [BV], doxorubicin, vinblastine, and dacarbazine) with bleomycin replaced by BV, a drug-conjugated anti-CD30 monoclonal antibody, to reduce toxicity. Patients with advanced and/or bulky disease frequently experience disease relapse, with reported recurrence rates at 5 years of ~20% in patients with early bulky disease and ~25% in those with progressive disease or advanced stage.[2] A significant number of relapsed/refractory (r/r) HL patients are ineligible for autologous stem cell transplantation (ASCT) or relapse after transplant and could benefit from anti-Programmed cell death protein 1 (PD-1) inhibitors, nivolumab and pembrolizumab, in monotherapy or in combination with BV with high tolerability, increased complete response rates, and durable remissions.[3]

In cHL, Reed-Sternberg cells express high levels of PD-1 ligands, thus favoring tumor escape as intratumor T cells become exhausted.[4] Therefore, PD-1 blockade by nivolumab prevents T-cell anergy and exhaustion while stimulating anti-tumor activity. PD-1 inhibition might induce an exaggerated immune response, causing distinctive inflammatory adverse effects, also known as immune-related (ir) adverse events (AEs), affecting multiple organs.[5] Here, we present the first reported case of an r/r cHL patient, treated with nivolumab after three lines of therapy, who achieved a complete hematological response while developing a rare form of retroperitoneal and mesenteric serositis successfully treated with surgery.

A 30-year-old male was diagnosed with cHL, lymphocyte depletion variant, stage III B/X at the Hematology and Transplant Center, University Hospital "San Giovanni di Dio Ruggi d'Aragona", Salerno, Italy, in November 2019. Because of the young age, OEPA polychemotherapy (vincristine, etoposide, and doxorubicin hydrochloride) was started. After two cycles of therapy, a PET scan re-evaluation showed disease persistence, and he was switched to the BeGEV regimen (bendamustine, gemcitabine, and vinorelbine) in February 2020. At re-evaluation, disease progression by PET scan was documented, and the ABVD regimen was initiated as third-line therapy in April 2020. Because of refractoriness, bleomycin was replaced with BV, obtaining a clinical response; however, after four cycles, the patient experienced grade IV hematological toxicity, and therapy was discontinued. In June 2020, a fourth-line therapy with BV and nivolumab was started, achieving a partial remission and allowing to perform an ASCT in October 2020. Because of high-risk disease and possible recurrence, he initiated a maintenance therapy with nivolumab in November 2020, based on published literature,[6] until May 2021, when he developed fever, abdominal pain, diarrhea, and severe thrombocytopenia. Steroids and immunoglobulins were quickly administered, resulting in fever resolution with persistence of thrombocytopenia. A bone marrow aspirate was performed to exclude disease recurrence or secondary acute leukemia, and eltrombopag was administered with subsequent benefits.

In September 2021, the patient complained of abdominal pain, and an ultrasound examination was carried out, showing a severe abdominal effusion with the presence of ~1500cc of free liquid extending along paracolic gutters, subphrenic, perihepatic, and perisplenic areas. A large-volume paracentesis was

performed, and effusion fluid appeared milky. Echocardiography, colonoscopy, and esophagogastroduodenoscopy were negative. CT scan, MRI, and lymphoscintigraphy were carried out, documenting thickening of mesentery root and omentum with some lymph node microgranulations at celiac-mesenteric and lumbo-aortic areas and along iliac-obturator and inguinal nodes with a slight increase of tracer uptake by PET examination. A diagnosis of mesenteric and retroperitoneal serositis of unknown origin was made, and the patient was in observational follow-up from June to December 2021. In May 2022, because of the persistence of this condition and a weight loss of ~15 kg in the last 4 months, he was sent to another Hospital for a highly specialized surgical consultation. Chyloperitoneum was resolved using a laparotomic approach for the identification of subdiaphragmatic areas of chylous leakage after a Servelle's test, consisting of the administration of a fatty meal four hours before surgery to identify chyliferous vessels and related intraperitoneal effusions easily. Next, specific chylolymphostatic treatment was performed by targeted anti-gravity ligatures, applications of biological adhesives, and synthetic fibrin patches. No postoperative complications were observed. Histology of intra-operative fragments documented the presence of an inflammatory tissue composed of fibro-angioblastic granulation tissue and histiocytes, reactive lymphocytes, and mesothelial cells without evidence of HL intra-abdominal localization. Therefore, a mesenteric and retroperitoneal serositis diagnosis was concluded as a nivolumab-related AE. After surgery, his clinical condition dramatically improved, and he is currently in complete response for HL, without symptoms.

To date, two monoclonal antibodies (nivolumab and pembrolizumab) targeting PD-1 have been approved for r/r HL, with overall response rates >60%, an excellent toxicity profile, and duration of response >1 year. However, these drugs can induce uncontrolled immune responses, leading to characteristic immune-related adverse events known as irAEs, mostly involving the gastrointestinal tract, endocrine glands, skin, and liver.[7] Previous multiple chemotherapeutic treatments and/or radiotherapy increase the risk of irAEs, as well as chronic use of anti-inflammatory agents. Management of severe irAEs requires drug discontinuation and high-dose steroids, while refractory AEs should be treated with other immunosuppressive agents, infliximab, or intravenous immunoglobulin.[8] Our case of r/r cHL treated with nivolumab as the fourth line of therapy followed by ASCT and maintenance therapy with the anti-PD-1 drug developed a rare nivolumab-induced mesenteric and retroperitoneal serositis resolved by surgical chyle-lymphatic treatment. This is the first-ever reported case of mesenteric and retroperitoneal serositis followed by nivolumab treatment in a r/r cHL, as previous cases have been described in solid tumors.[9] Our patient had several risk factors for irAE, such as advanced (stage III) and multi-refractory disease. Moreover, previous cases mostly describe pericardial effusions with subsequent pericardial tamponade, with recurrence in 19% of cases despite drug discontinuation.[10]

Clinical management is challenging, and these irAEs have been mainly treated with checkpoint inhibitor discontinuation, pericardiocentesis for pericardial effusion, and steroids with benefits in less than 50% of cases.[9] However, recurrence is frequent, and repeated punctures or second-line immunosuppression (e.g., with infliximab) are required.[10] Here, we first attempted steroids, intravenous immunoglobulins, and eltrombopag, which improved fever, diarrhea, and thrombocytopenia while not ascites. Then, highly specialized surgery was required for chyle-lymphostatic treatment that successfully and completely resolved the symptomatology. Indeed, at the time of writing, the patient is still in complete remission for his hematological disease, and no new episodes of serositis were reported.

In conclusion, checkpoint inhibitors can cause autoimmune adverse events affecting any organs and tissues, such as serositis. This immune-related serositis in an r/r cHL, refractory to steroids and intravenous immunoglobulins, was successfully treated with chyle-lymphostatic surgery, preventing adverse event recurrence. Considering the increasing use of nivolumab in the future, identifying irAE biomarkers for differential diagnosis and specific guidelines for clinical management are necessary to improve outcomes of these drug-related toxicities.

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Ethical approval. Protocol was approved by the local ethics committee (Ethics Committee "Campania Sud", Brusciano, Naples, Italy; prot./SCCE n. 24988).

Informed consent. The patient received informed consent in accordance with the Declaration of Helsinki (World Medical Association 2013) and protocols approved by the local ethics committee (Ethics Committee "Campania Sud", Brusciano, Naples, Italy; prot./SCCE n. 24988).

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Matteo D'Addona[1,#], Luca Pezzullo[2,#], Corradino Campisi[3], Corrado Cesare Campisi[4,5], Valentina Giudice[1,2], Vincenzo Ciccone[6], Roberto Guariglia[2], Bianca Serio[2] and Carmine Selleri[1,2].

[1] Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Baronissi 84081, Salerno, Italy.
[2] Hematology and Transplant Center, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno 84131, Salerno, Italy.
[3] Research Center & Scientific Section Clinical Lymphology, Lymphatic Surgery & Microsurgery-Department of Surgical Sciences and Integrated Diagnostics-DISC, School of Medical Sciences & Pharmaceutics-University of Genova, Genoa, Italy.
[4] Plastic, Reconstructive and Lymphatic Surgery, GVM Care & Research, Genoa, Italy.
[5] Plastic Surgery, Department of Medicine, University of Catania, Italy.
[6] Radiology Unit, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno 84131, Salerno, Italy.
[#] The authors equally contributed to the work.

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Correspondence to: Carmine Selleri. Tel.: +39-089673150; Fax.: +39-089673153. E-mail: cselleri@unisa.it

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