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Granulomatous mesenteric lymphadenitis after three doses of the COVID-19 vaccine

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Abstract

Lymphadenopathy related to vaccination has been reported as an adverse effect of mRNA-based COVID-19 vaccines. Most cases are regional lymph nodes near of injection site, with mild-moderate 18 F-fluorodeoxyglucose uptake on positron emission tomography. We report a middle-aged Brazilian man with mesenteric lymphadenitis manifested five days after the third dose of the Pfizer-BioNTech mRNA-based vaccine against COVID-19. The patient had no known risk factors and evolved with rapid clinical improvement. The imaging findings, laboratory determinations, histopathological and microbiological evaluations raised doubts about the hypothesis of an eventual adverse effect of the vaccine. The aim is to call attention to possible rare reactions of SARS-CoV-2 vaccinations.

Key word: COVID-19, granulomatous reaction, mesenteric lymphadenitis, vaccine.

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Introduction

Lymphadenitis in axillary, supraclavicular, infraclavicular, subpectoral, and neck regions are often reported following the SARS-COV-2 vaccination (1-6); some case studies of patients with abdominal lymphadenopathy have also been described (1,3,5). Usual manifestations of COVID-19 infection include fever, headache, weakness, cough, dyspnea, myalgias, nausea, vomiting, diarrhea, rhinorrhea, anosmia, and ageusia (1,3).

Abdominal lymphadenopathy may also occur during multisystem inflammatory syndrome 2-6 weeks after the severe acute COVID-19 infection or vaccination (6). Because of the high expression of angiotensin-converting enzyme 2 and transmembrane serine protease 2 receptors on the surface of enterocytes, vaccines may be a local trigger for immune-mediated inflammatory response giving origin to the adenomesenteritis (1). Nowadays, children five years and older undergo the BNT162b2 messenger RNA COVID-19 vaccine, but knowledge about possible adverse events is still scarce (1). Therefore, reports of unusual adverse reactions to the vaccines are paramount. The main objective of this paper is to comment on a possible and scarcely described complication of COVID-19 vaccination, which manifests as mesenteric lymphadenitis.

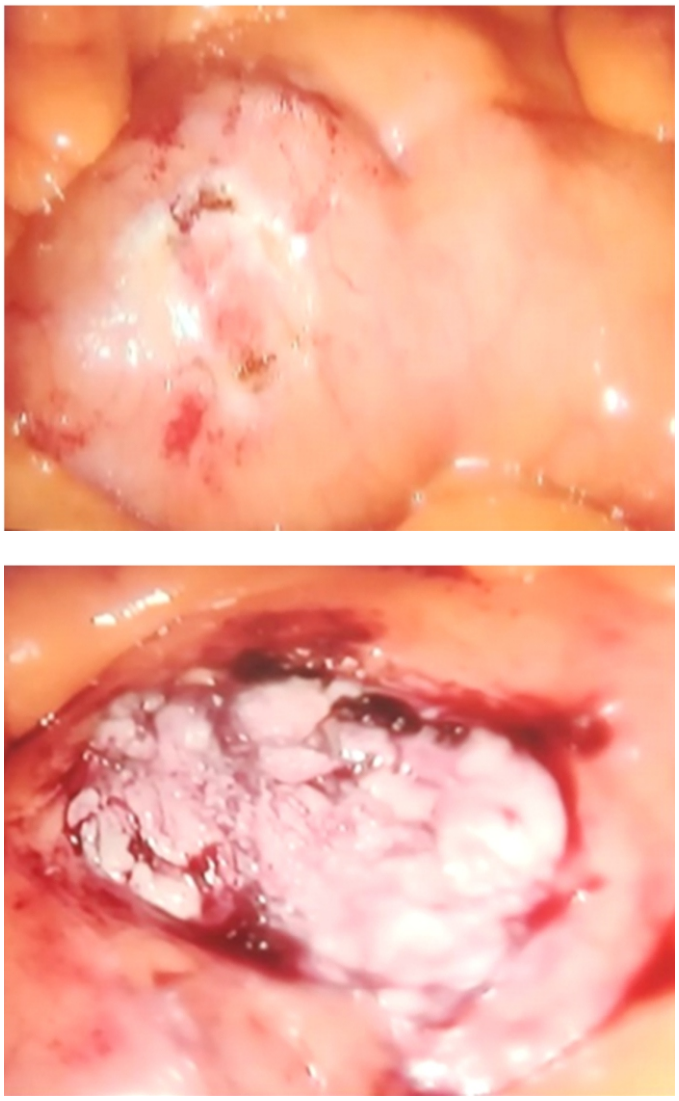
Clinical case

Five days after the third dose of the Pfizer-BioNTech mRNA-based vaccine against COVID-19, a middle-aged Brazilian male presented with moderate abdominal pain followed by fever (up to 390C) for a week, which was relieved by oral dipyrone.

Besides, he underwent clinical, laboratory, and imaging evaluations to clarify the diagnosis. The laparoscopic study of the upper abdomen and pelvis showed clusters of mesenteric lymph nodes in the mesogastrium measuring 9.6 cm x 4.6 cm (Figure 1) and right flank with central necrosis and inflammatory reaction in the adjacent fat; in addition to lymph node enlargement in the left external iliac chain (the largest measuring 3.2 cm x 2.1 cm). The macroscopic appearance of the abdominal viscera was normal, while a laparoscopic biopsy of abnormal mesenteric lymph nodes resulted in six yellowish-brown elastic samples measuring 3.0 cm x 1.5 cm x 1.5 cm. The pathologic studies revealed a typical pattern of granulomatous lymphadenitis, necrosis, multinucleated cells, and epithelioid palisade. The searches for acid-fast bacilli (Fite-Faraco) and fungi (Periodic acid-Schiff and Grocott) resulted in negatives in the samples of the studied lymph nodes. Both the Mantoux test and the QuantiFERON TB Gold IGRA test were non-reactive; nevertheless, following the Infectologist opinion, he underwent the schedule of isoniazid and rifampicin for six months, plus pyrazinamide and ethambutol during the first two months. The longstanding follow-up and the abdominal imaging of control were unremarkable.

Figura 1

Laparoscopic images taken before and after the biopsy showed a cluster of mesenteric lymph nodes sited in the mesogastrium, measuring 9.6 cm x 4.6 cm



Discussion

In this setting, one should consider recent literature data about mesenteric lymphadenitis associated with SARS-CoV-2 infection and COVID-19 vaccination. Chua TH and Takano A (2022) performed a systematic review of the pathological findings reported in patients with lymphadenopathy related to COVID-19 vaccination (2). Twenty-five studies involved the COVID-19 vaccination, and 14 others were related to non-COVID-19 vaccines. The pooled analysis of 21 studies included 37 patients (47.8 ± 19.1 years old), and 62.2% were female; 24.3% had no medical antecedent, and 21.6% had prior melanoma, breast cancer, lung cancer, appendix neuroendocrine tumor, Merkel cell carcinoma, and renal cancer. Most cases occurred after the first dose of the Pfizer-Bio-NTech vaccine; other vaccines were Moderna, AstraZeneca, Vaxzevria, and CureVac (2). The commoner sites of lymphadenopathy were in supraclavicular (46.2%), axillary (30.8%), and cervical (23.0%) areas, with symptoms such as fever (46.2%) and pain (30.8%). The time from the last vaccination to the diagnosis of lymphadenopathy was 14.5 ± 11.0 days. Abnormal lymph node findings were reported using ultrasound (29.7%), computed tomography/magnetic resonance (29.7%), and PET/CT (21.6%). Lymph node changes were reactive or non-malignant (75.5%), besides Kikuchi-Fujimoto disease (8.1%), lymphoid hyperplasia (5.4%), granulomatous reaction (5.4%), or metastases (5.4%). Noteworthy was the absence of lymphadenopathy with a site in the abdominal cavity (2). Kesharvaz et al. (2021) reviewed the data of case studies of 60 women and eight men with lymphadenopathy after first or second dosages of Pfizer-BioNTech (44.1%), Moderna (25%), and Oxford-AstraZeneca (1.5%), and 29.4% cases only cited as mRNA COVID-19 vaccines (4). The age range was 32 to 76 years, and 82.3% had prior or active malignancy: breast cancer (n = 40), myeloma (n = 2), liposarcoma (n = 1), lymphoma (n = 2), lung cancer (n = 4), melanoma (n = 4), cervical cancer (n = 1), parotid cancer (n =1), and oral carcinoma (n = 1). The median time of diagnosis after the first or second dose was 12 and 5 days, respectively, and images were from day 1 to 4 weeks after vaccination, remaining for 5 and 6 weeks of the first and second doses. Lymph nodes were in the axillary (82.3%), supraclavicular (11.4%), infraclavicular (1.2%), and subpectoral or neck region (5.1%). Features of the lymph nodes included cortical thickening, irregular nodal cortex, preserved hilar fat, and increased FDG uptake with mean SUV max of 6.8 ± 3.4 g/ml. There was no description of abnormalities involving intra-abdominal lymph nodes (4). Bloise S et al. (2022) described a 13-year-old female with a five-day fever (up to 39.5°C), which appeared less than 12 hours after the first dose of the BNT162b2 vaccine and was associated with headache, abdominal pain, vomiting, and two episodes of diarrhea (1). Physical examination was unremarkable, except for fever and slight tenderness on the abdomen, and both the antigen and molecular swabs for SARS-CoV-2 resulted in negative. The abdominal ultrasound images detected the presence of enlarged lymph nodes and mesenteric inflammation, considered consistent with the diagnosis of adenomesenteritis. Her clinical condition improved in three days during admission, and the control ultrasound showed a

reduction of mesenteritis and lymph node alterations. Besides, she performed specific laboratory tests for COVID-19, which showed positivity for IgG (32.77 AU/mL, cutoff of normality <10) and COVID-19 IgM negative (0.92 AU/mL). The authors emphasized her remarkable history of prior SARS-CoV-2 infection in January 2020, characterized by a fever lasting for three days and recurrent headache symptoms. In fact, adenomesenteritis may develop in acute SARS-CoV-2 infection as well as in the Multisystem inflammatory syndrome that appears 4-6 weeks after primary infection (1). The patient had a negative nasopharyngeal swab and IgM for SARS-CoV-2, and more than ten months since the primary infection, ruling out both reinfection and the syndrome. Gastrointestinal involvement by long Covid was also discarded because the major symptoms are vomit and diarrhea with a chronic-recurrent course and not an acute onset. The temporal relationship with vaccination indicates that the adenomesenteritis was due to the role of the m-RNA vaccine on the immune response with lymph node involvement (1). Iftikhar H et al. (2021) reported an adult male with severe abdominal pain and tenderness in the right inguinal fossa (3). The laboratory routine and the chest images were normal, but COVID-19 PCR was positive, and the abdominal CT revealed enlarged lymph nodes. He had poorly controlled diabetes mellitus, arterial hypertension, and hyperlipidemia. Despite the risk factors, his clinical evolution was uneventful after hospital discharge; the abdominal pain in this scenery usually subsides in up to 3 weeks. Authors highlighted the need for careful differential diagnosis in emergency services because mesenteric lymphadenitis more often affects younger people and mimics acute appendicitis or intussusception but can be a presentation in adults with COVID-19 (3).

In the present case, the manifestations started five days after the third dose of the Pfizer-BioNTech vaccine, differing from the majority of the reported patients, who had lymphadenitis 14.5 ± 11.0 days after receiving the first dose of this same kind of vaccine; besides, the granulomatous reaction has been uncommon, described in 5.4% of cases (2).

Reports of vaccine-associated lymphadenopathy have been more common, with case studies including histopathology and imaging correlation, and hypermetabolic lymph nodes may be found distant from the vaccine site, including the abdomen. Careful control of immunized people is needed, mainly because the vaccines are administered to children. In the present case, although with the time relationship, there is no conclusive evidence confirming a causal relation between mesenteric lymphadenitis and vaccination. Additional concerns are on scarce data of complete necropsy studies and the possibility of under-detected or underreported cases of abdominal lymphadenitis in COVID-19.

Author contributions

The authors confirm their contribution to the paper as follows: study conception and design: Vitorino M. dos Santos, Lister A. M. dos Santos, Laura C. Modesto, Julia C. Modesto; data collection: Vitorino M. dos Santos, Lister A. M. dos Santos, Laura C. Modesto, Julia C. Modesto; analysis and interpretation of results: Vitorino M. dos Santos, Lister A. M. dos Santos; draft manuscript preparation: Vitorino M. dos Santos. All authors reviewed the results and approved the final version of the manuscript. All authors agreed to be responsible for all aspects of the work to ensure the accuracy and integrity of the published manuscript.

Ethical Statement

For the presentation of this letter, we had the approval and informed consent of the patient. In writing the manuscript, the authors followed the Committee on Publication Ethics (COPE) policy.

Conflict of interest

The authors declare no conflicts of interest.

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