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COVID-19 vaccine-associated lymphadenopathy: a review

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SUMMARY

Following the introduction of RNA-based vaccines, COVID-19 vaccine-associated clinical lymphadenopathy (C19-LAP) has been reported as a side effect. Moreover, subclinical lymphadenopathy detected on imaging (SLDI) has also been observed, mainly as incidental findings while performing screening tests on oncological patients. In these cases, surgical lymphadenectomy, fine-needle aspiration cytology (FNAC) and core needle biopsy (CNB) have been used as a valuable diagnostic tool for SLDI and C19-LAP. In this review the clinical, histologic and cytologic features of SLDI and C19-LAP have been investigated. A search for studies that reported on C19-LAP and SLDI histopathology and cytopathology was performed on PubMed and Google Scholar, on 11 January 2023. Thirty-one reports on SLDI and C19-LAP were retrieved and included in a pooled analysis. In total, we included 54 patients with a median age of 47 years. In our research, surgical excision, CNB and/or FNAC of C19-LAP or SLDI enlarged lymph nodes have been performed in 54 cases. Of all cases, only two metastases were diagnosed and one case was diagnosed as reactive hyperplasia with atypical follicles. The remaining cases were reactive lymphadenopathy (28 cases), follicular hyperplasia (13 cases), Kikuchi-Fujimoto disease (6 cases), granulomatous lymphadenitis (2 cases), eosinophilic lymph node abscesses (1 case), Langherans cell histiocytosis (1 case), Rosai-Dorfman disease (1 case). SLDI and C19-LAP have represented a diagnostic dilemma, especially in oncologic patients. The role of different diagnostic tools for SLDI and C19-LAP has been discussed.

Keywords: COVID, vaccine, lymphadenopathy, histology, cytology.

INTRODUCTION

Whereas the COVID-19 has not been the first pandemic in human history, it has shown unique features in terms of diffusion and direct and indirect effects. Different vaccines have been produced and used in mass vaccination programs, with different modalities and different levels of efficacy on the populations for each country [1, 2]. Moreover, SARS-CoV-2 vaccines have been the first mRNA vaccines to be approved for clinical application. COVID-19 vaccines have been demonstrated to be safe and effective, with significant reduction in symptomatic COVID-19 in older adults, and with further protection against severe disease; however, some adverse effects have been reported [1-3]. Different COVID-19 vaccines have been developed. COVID-19 vaccines are commonly administered intramuscularly in the upper arm at determined intervals in at least two shots [2, 4]. As with any other vaccines, COVID-19 vaccine may cause side effects, the most common being local pain and inflammation at the injection site, fatigue, headaches, fever, chills, and muscle and joint pains, often registered after the first administration, also depending on the vaccine type and individual responsivity [2,

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5-16]. Post-vaccinal lymphadenopathy due to reactive changes in the lymph nodes is well known and has been described as consequence of different vaccines including bacillus Calmette–Guerin (BCG), hepatitis B, human papillomavirus, and tetanus amongst several others [5-22]. COVID-19 vaccine-associated lymphadenopathy (C19-LAP) may also occur, mostly reported in axillary, clavicular or cervical lymph nodes, after vaccine inoculation in the arm. In the Pfizer BioNTech COVID-19 vaccine trial, the axillary and supraclavicular C19-LAP incidence occurring in the same side of injection was 0.3% for the vaccine group versus <0.1% for the placebo group [16, 22]. In the case of the Moderna vaccine trial, the incidence was 1.1% [16, 22]. The site of lymphadenopathy was axillary in 11% of the patients after the first dose, and 16% after the second dose of Moderna vaccine; similar data has been reported after the Comirnaty-Pfizer/BioNTech vaccine [23, 24]; Caputo et al. summarized the incidence of C19-LAP for each of COVID-19 vaccines (Table 1) [23-25]. C19-LAP is probably just the epiphenomenon of lymph node reactivity, since COVID-19 vaccine-associated subclinical lymphadenopathy (SLDI) has been reported in a higher percentage of cases when compared to C19-LAP [22]. The detection of C19-LAP is mainly clinical and can be confirmed by ultrasound (US). Combined clinical data and US features allow the diagnosis of reactive SLDI or C19-LAP; hence, just a clinical follow-up is appropriate in most cases. Nonetheless, some C19-LAP and SLDI mimicked malignant lymphadenopathies, raising differential diagnostic problems [26-32]. In these cases, a pathological evaluation of lymphadenopathy has been performed in a number of cases. A review of the pathological features of C19-LAP was performed by Chua et al. [14]. This review focused on the reported histopathological features of C19-LAP up to the 2021. Nonetheless, other than histopathology, core-needle biopsy (CNB) and fine-needle aspiration cytology (FNAC) may be used for both reactive processes and lymphoma or metastases and have been utilized to assess LAP during the pandemic [6, 25, 32-39]. In this study, a review of C19-LAP reports between January 2021 up to December 2023 has been performed including both cytological and histopathological reports which were analyzed according to the lymphadenopathy and vaccines types.

MATERIALS AND METHODS

A literature search was initially performed through PubMed and Google Scholar, on 11 January 2024, with the following keywords: 'COVID', 'vaccine', 'lymphadenopathy', 'histology', 'cytology', and 'fine-needle aspiration'. During the search, the authors placed no restrictions on the year of publication and searched reference lists of full-text articles, mainly those of systematic reviews for additional studies that were not identified in the initial search. Only literature published in English was selected, including studies that reported histopathological and/or cytological findings in COVID-19 vaccine-related lymphadenopathy [22, 25-34, 41-67]. Studies on SLDI, mainly detected by US or 18F-FDG PET-CT were also selected and used for a general comprehension and description of the phenomenon and to retrieve cases evaluated by histology or LN-FNAC [68-77]. Recommendation articles, protocols, commentaries, and non-English articles were not considered. Data extracted from studies regarding C19-LAP and SLDI included the following: type of publication, number of patients and clinical data, type and dose of administered vaccine, delay from last vaccination to lymphadenopathy, LN site and size, histological and cytological features, management and outcome.

COVID-19-vaccines lymphadenopathy

Whereas post-vaccinal LAP is a quite rare event, the majority of COVID-19 vaccines may cause reactive lymphadenopathy, which usually is subclinical and an occasional finding; nonetheless, in a minority of cases, C19-LAP may be clinically evident. In fact, 36% of cases presented increased lymph node 18F-FDG uptake up to 10 weeks after vaccination, with women and people over 65 years being most frequently affected [75, 76]. Lymph node enlargement has been reported in ~1% of the COVID-19 vaccinated, more specifically in 0.3% of Pfizer-BioNTech and 1.1% of Moderna vaccines, respectively (Table 1) [16, 41, 64]. While most SLDI do not show clinically evident lymph nodes enlargement, the awareness of physicians about SLDI is fundamental, especially in case of cancer staging or follow-up to avoid the risk of overdiagnosis.

Patients' Characteristics

The present study is a pooled review based on 31 reports [25-28, 30-34, 41-45, 47-56, 58, 59, 61-65, 68].

Table 1 - Main COVID-19 vaccines and corresponding lymphadenopathy as side effects, as reported by Caputo et al. [33]. The table was included with the permission of the authors.

Name	*Type*	*Preparation*	*Dosage*	*Incidence of lymphadenopathy*
Comirnaty (Pfizer Inc & BioNTech)	mRNA	S-Protein	2 doses, 21 days apart	3-9% (69)
mRNA-1273 (Moderna)	mRNA	S-Protein	2 doses, 28 days apart	1.1% (33)
COVID-19 Vaccine Janssen (Johnson & Johnson)	Viral Vector Vaccine	Type 26 human adenovirus	COVID-19 Vaccine Janssen	Not available
COVID-19 vaccine (AZD1222) (Oxford/AstraZeneca)	Viral vector vaccine	Adenovirus vector	NR	<1% (69)
Vaxzevria (Oxford/AstraZeneca)	Modified Adenovirus	Modified adenovirus	NR	4 cases (69,73)
CoronaVac (Sinovac)	Inactivated virus	Whole virus inactivated	2 doses, 28 days apart	Not available
Covaxin (Bharat Biotech)	Viral Vector Vaccine	S-Protein	2 doses, 28 days apart	Not available
Covishield (Oxford-AstraZeneca)	Viral Vector Vaccine	S-Protein	2 doses, 3 months apart	Not available
Nuvaxovid (Novavax)	Protein Subunit	Long S-Protein	2 doses, 21 days apart	Not available

In total, 54 cases are reported, including 43 (80%) females, 10 (18%) males, and one patient whose gender was not reported; the median age was 47 years. Previous or active history of different malignancies was reported in 24 cases (44%), which included breast cancer, renal cell carcinoma, melanoma, oral squamous cell carcinoma, neuroendocrine tumor (NET) or lung carcinoma or had a positive family history of breast carcinoma (2 cases, 4%) [21]. C19-LAP was reported after first, second or third administrations of the vaccine; Pfizer-BioNTech (40 cases, 74%) and Moderna (7 cases, 13%) were the most frequently used, followed by Vaxzevria (2 cases) and Astra-Zeneca (1 case), CureVac (1 case); in 1 case, vaccine type was reported as mRNA COVID-19 vaccine, while in 2 cases vaccine type was not reported. C19-LAP was observed in imaging examinations and after the first, second and third administrations of Pfizer-BioNTech vaccine; the time interval between the vaccine administration and the onset of the lymphadenopathy was reported in 35 out of 41 cases (85%), with me-

Table 2 - Clinical data of COVID-19 vaccines-related lymphadenopathies from 31 reports.

Reference	*# Case*	*Sex*	*Age*	*Clinical History*	*Dose, Vaccine, Onset (days)*
Aalberg JJ [27]	1	NR	74	Stage IV renal carcinoma	1st, Moderna, 63
Trikannad A [65]	1	F	57	Melanoma	1st, Pfizer Inc & BioNTech, 21
Gullotti DM [26]	1	M	53	Negative	2nd, Pfizer Inc & BioNTech, NR
Heaven CL [50]	4	M	42	Negative	1st, Pfizer Inc & BioNTech, 4
		F	34	Psoriatic arthritis	2nd, Pfizer Inc & BioNTech, 7
		F	70	Negative	2nd, Pfizer Inc & BioNTech,76
		M	45	Negative	1st, Pfizer Inc & BioNTech, 31
Garcia-Molina F [42]	4	F	34	NR	1st, Pfizer Inc & BioNTech, 5
			27		
			42		
			42		
Dirven I [34]	1	F	60	MEN1	1st, Pfizer Inc & BioNTech, 21

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Reference	*# Case*	*Sex*	*Age*	*Clinical History*	*Dose, Vaccine, Onset (days)*
Tan NJH [43]	1	M	34	Negative	1st, Pfizer Inc & BioNTech, 1
Cardoso F [51]	1	F	48	Family history of breast cancer	1st, Pfizer Inc & BioNTech, 14
Fernández-Prada M [52]	5	F	Mean 44	NR	1st, Pfizer Inc & BioNTech, 1-24
Kang ES [28]	1	M	59	Oral squamous carcinoma	NR, Moderna, 14
Yoshimoto N [53]	1	F	70	Breast, colon carcinomas	NR
Yu Q [41]	1	F	34	Negative	NR
Ganga K [58]	1	M	40	Arterial hypertension	2nd, Moderna, NR
Hagen C [44]	5	M	66	Lung carcinoma	2nd, Moderna, 41
		F	41	Negative	1st, Moderna, 76
		F	47	Negative	1st, Pfizer Inc & BioNTech, 22
		F	47	NET appendix	1st, Moderna, 63
		M	52	Lung carcinoma	2nd, Pfizer Inc & BioNTech, 42
Betancur V [47]	1	F	45	Negative	2nd, Pfizer Inc & BioNTech, 42
Daghri S [48]	1	F	24	Negative	2nd, mRNA vaccine, 30
Kaya A [49]	1	F	37	Allergic asthma	1st, Pfizer Inc & BioNTech, 10
Ikeda K [55]	1	F	20	Negative	1st, Pfizer Inc & BioNTech, 10
Ashoor A [30]	1	F	61	High-grade DCIS	2nd, AstraZeneca, 1
Eifer M [31]	1	F	41	Breast cancer	1st, Pfizer Inc & BioNTech, 22
Ozutemiz K [61]	2	F	46	Breast cancer	2nd, Pfizer Inc & BioNTech, 7
			38	Family history of breast cancer	1st, Pfizer Inc & BioNTech, 8
Lim J [64]	3	F	61	Breast cancer	1st, Vaxzevria, 16
			71		1st, Vaxzevria, 8
			75		2nd, Pfizer Inc & BioNTech, 14
Giorgis S [32]	5	F	66	Breast cancer	NR, Pfizer Inc & BioNTech, 30
			46		
			76		
			59		
			54	Family history of breast cancer	
Tripathy S [33]	1	F	61	Lung carcinoma	2nd, Pfizer Inc & BioNTech, 14
Caputo A [25]	1	F	58	Breast cancer	2nd, Pfizer Inc & BioNTech, 14
Placke [56]	2	F	28	Melanoma	1st, Pfizer Inc & BioNTech, 28
			43		2nd, Pfizer Inc & BioNTech, 50
Kado S [59]	1	F	31	Negative	1st, Pfizer Inc & BioNTech, 8
Al Soub HA [62]	1	M	18	Nephritis	1st, Pfizer Inc & BioNTech, 10
Tan HM [45]	2	F	18	Negative	1st, Pfizer Inc & BioNTech, 42
		M	24	Diabete mellitus, hypertension	1st, Pfizer Inc & BioNTech, 17
Tintle S [63]	1	F	23	Asthma, eczema, hypothyroidism	2nd, Moderna, 7
Patil A [68]	1	F	70	Breast cancer	3rd, Pfizer Inc & BioNTech, 30

dian delay of 18.4 days (range, 1-76 days). As for Moderna, the median delay time was reported in 6 out of 7 cases (86%) and it was 44 days (range, 7-76). The median delay time for Vaxzevria was of 12 days, (range 8-16). Corresponding data are summarized in Table 2.

Histological and/or cytological examination was performed on 55 different lymph nodes. Reported lymphadenopathies were axillary (28 cases), supraclavicular (12 cases), cervical (6 cases), submandibular (3 cases), mediastinal (1 case), retro-auricular (1 case), inguinal (1 case) and scapular (1 case); lymphadenopathy site was not reported in 1 case (2%). All the lymph nodes were first evaluated by imaging, most frequently by ultrasound (US) and reported as enlarged, oval, usually hypoechoic, with major diameters ranging from 10 to 50 mm (mean 15.7); spherical shape was reported in 4 cases [44, 51, 63, 64]. Another reported US feature was diffuse or focal cortical thickening and preserved, visible hilum in almost all the cases. Increased standardized uptake value (SUV) was reported in 5 cases; effaced hilum was reported in one case [31, 33, 44, 56, 61, 68].

C19-lap pathological features

Surgical excision, CNB and/or FNAC of C19-LAP or SLDI have been performed in 54 cases [25-28, 30-34, 41-45, 47-56, 58, 59, 61-65, 68]. The pathological diagnoses were reactive lymphadenopathy (28 cases), follicular hyperplasia (13 cases), eosinophilic lymph node abscesses (1 cases), reactive hyperplasia with atypical follicles (1 case), granulomatous reaction (2 cases), metastases (2 cases), Kikuchi-Fujimoto disease (KFD) (6 cases), Langerhans cell histiocytosis (LCH) (1 case) [25, 27, 28, 30-32, 34, 41, 42, 44, 45, 47-52, 53, 56, 58, 59, 61-64, 65, 68]. In cases of reactive hyperplasia, the pathologist report described a preserved lymph node structure with cortical follicular hyperplasia, enlargement of germinal centers and interfollicular expansion by small lymphocytes. Prominent germinal centers and tingible-body macrophages were frequently reported; moreover, capillaries with focally prominent endothelial cells have been described in the expanded interfollicular regions [61]. Capsule thickening was frequently reported. The immunohistochemical phenotype (IHC) was reported in 12 cases [25, 26, 33, 42, 43, 45, 47, 48, 51-53, 55, 68]. Flow cytometry was reported in 7 cases [33, 42, 44, 51, 63]. Heaven et al. reported four cases of reactive lymphadenopathy: FNAC showed polymorphous lymphoid cells suggestive of a reactive process and the following histological examination confirmed the diagnoses [50]. Surgical excision was performed, assessing a polyclonal reactive process. Eifer et al. reported a case of axillary lymphadenopathy in a 41 years old woman with newly diagnosed breast cancer; hematoxylin- and eosin-stained images of cores of lymph node tissue showing prominently dilated and edematous sinuses that probably reflect reactive changes [30]. Ozutemiz et al. described a case of post-vaccine lymphadenopathy in a 46 years old woman with a history of breast cancer [61]. Histopathology was consistent with reactive lymph nodes. García-Molina F et al. reported 2 cases of nonspecific chronic adenitis [42]. Tan NJH et al. described one case of reactive follicular hyperplasia [43]. Fernández-Prada M et al. reported 5 cases showing reactive inflammatory signs, with lymphocytic infiltrate and active germinal centers [52]. Patil et al. described a case of atypical follicular hyperplasia with light chain–restricted germinal centers after COVID-19 Pfizer-BioNTech vaccine booster [68]. In histologic section, lymph node contained prominent and abnormal secondary lymphoid follicles, which showed ill-defined borders, poorly defined to absent mantle zone, lack of germinal polarization and contain a relatively monotonous population of medium- to large-sized centrocytic and centroblastic lymphoid cells with decreased apoptotic bodies and no tingible body macrophages. Kaya et al., instead, reported a case of C19-LAP with eosinophilic abscesses observed in a 37 years old female patient with a history of allergic asthma [49]. COVID-19 associated KFD have been described as typical histological features of corresponding, non-vaccinal related entities [45, 47, 48, 55, 62]. Core needle biopsies of lymph nodes showed multifocal necrotizing lymphadenopathy characterized by foci of necrosis surrounded by reactive appearing small lymphoid cells, histiocytes and plasma cells. Placke et al. and Trikannad et al. both reported a case of granulomatous reactive process in patients undergoing staging for melanoma [56, 65]. Tintle et al. reported the histological features of a case of post-vaccination Langerhans cell hyperplasia in a 23-years-old woman [63]. The authors reported focal aggregates of LCs, dendritic cells, and histiocytes with rare images of hemophagocytosis. Gullotti et al. and Tripathy et al. reported me-

tastases for melanoma and lung cancer, respectively diagnosed by FNAC [26, 33].
In summary, pathological evaluation of SLDI and C19 LAP has been performed during the follow-up for different neoplasms in 24 patients, in 6 patients with comorbidity, in 15 cases with negative clinical history and in 9 cases in which patients' clinical history was not reported. Clinical and pathological features of the reported cases are summarized in Table 3.

Table 3 - Imaging and pathological features of COVID-19 vaccine related lymphadenopathies from 31 reports.

Reference	*# case*	*Lymph node site/size (mm)*	*Imaging*	*Pathological features*	*Follow-up*
Aalbeeg JJ [27]	1	Axillary L/23	Oval, preserved hilum, thickened cortex	Reactive lymphadenopathy	Clinical
Trikannad A [65]	1	Mediastinal/23	NR	Granulomatous lymphadenitis	Clinical
Gullotti DM [26]	1	Axillary L/50	Round, hypoechoic	Metastasis, melanoma	Clinical
Heaven CL [50]	1	Supraclavicular/NR	NR	Follicular hyperplasia	Clinical, negative
	3	Submandibular L/NR	NR	Reactive lymphadenopathy	Clinical
		Supraclavicular L/10			Clinical, negative
		Submandibular L/NR			NR
Garcia-Molina F [42]	4	Supraclavicular/NR	Oval, increased vascularization	Reactive lymphadenopathy	Complete resolution after anti-inflammatory therapy
		Axillary/NR	NR		
Dirven I [34]	1	Axillary/NR	NR	Reactive lymphadenopathy	Clinical, complete resolution
Tan NJH [43]	1	Supraclavicular L/11	Oval, hilum not clearly visualized	Follicular hyperplasia	Clinical, complete resolution
Cardoso F [51]	1	Cervical R/14	Round, ill-defined hilum, hypoechogenic	Follicular hyperplasia	NR
Fernández-Prada M [52]	5	Supraclavicular L/NR	NR	Reactive lymphadenopathy	NR
Kang ES [28]	1	Bilateral cervical/NR	NR	Reactive lymphadenopathy	NR
Yoshimoto N [53]	1	Cervical/NR	Oval, maintained US structure	Reactive lymphadenopathy	Clinical, complete resolution
Yu Q [41]	1	Axillary L/40	Oval, hypoechoic, thickened cortex	Reactive lymphadenopathy	NR
Ganga K [58]	1	Submandibular L/50	Round, hypoechoic	Reactive lymphadenopathy	Clinical, negative
Hagen C [44]	5	Axillary L/NR	Oval to round, only partially detectable hilum	Follicular hyperplasia	Clinical, negative
		Infraclavicular L/NR			
		Supraclavicular L/NR			
		Cervical L/NR			
		Retroclavicular L/NR			
Betancur V [47]	1	Axillary R/25	Thickened cortex, irregular margins	Kikuchi-Fujimoto lymphadenitis	Clinical
Daghri S [48]	1	Laterocervical bilateral/15	Multiple, enlarged	Kikuchi-Fujimoto lymphadenitis	Complete resolution after anti-inflammatory therapy

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Reference	*# case*	*Lymph node site/size (mm)*	*Imaging*	*Pathological features*	*Follow-up*
Kaya A [49]	1	Axillary L/26	Multiple, enlarged	Eosinophilic lymph node abscess	Complete resolution after anti-inflammatory therapy
Ikeda K [55]	1	Inguinal R/NR	Multiple, enlarged	Kikuchi-Fujimoto lymphadenitis	Complete resolution after anti-inflammatory therapy
Ashoor A [30]	1	Axillary L/NR	Thickened cortex	Reactive lymphadenopathy	NR
Eifer M [31]	1	Axillary L/NR	Increased SUV	Reactive lymphadenopathy	NR
Ozutemiz K [61]	1	Axillary/20 Clavicular/13	Thickened cortress, increased SUV	Follicular hyperplasia	NR
	1	Axillary L/NR	Thickened cortress	Follicular hyperplasia	NR
Lim J [64]	1	Axillary L/NR	Thickened cortress	Reactive lymphadenopathy	NR
	1	Axillary L/NR	Smooth and diffuse enlargement		
	1	Axillary L/NR	Multiple, enlarged, round		
Giorgis, S [32]	1	Axillary L/22	Maintained US structure	Reactive lymphadenopathy	NR
	1	Axillary L/23	Thickened cortress		
	1	Axillary L/13	Thickened cortress		
	1	Axillary R/20	Maintained US structure		
	1	Axillary L/20	Maintained US structure		NR
Tripathy S [33]	1	Retroauricular R/15	Increased SUV	Metastasis, lung cancer	Clinical
Caputo A [25]	1	Cervical R/12	Oval, hypoechoic, preserved hilum	Follicular hyperplasia	Clinical, negative
Placke [56]	1	Axillary L/16	Increased SUV	Follicular hyperplasia	Clinical
	1	Axillary L/10	Enlarged, preserved hilum	Granulomatous lymphadenitis	Sclerotherapy
Kado S [59]	1	Scapular L/NR	Round, no hilum	Follicular hyperplasia	Clinical, negative
Al Soub HA [62]	1	Supraclavicular L/11	Multiple, enlarged	Kikuchi-Fujimoto lymphadenitis	NR, negative
Tan HM [45]	1	Axillary L/20	Multiple, enlarged	Kikuchi-Fujimoto lymphadenitis	NR
	1	Axillary L/32	Multiple, enlarged	Kikuchi-Fujimoto lymphadenitis	NR
Tintle S [63]	1	Axillary L/21	Multiple, enlarged	Langerhans cell hyperplasia, hemophagocytosis	Complete resolution after anti-inflammatory therapy
Patil A [68]	1	Axillary R/12	Multiple, enlarged, cortical thickening, increased SUV	Reactive hyperplasia with atypical follicles	Clinical, negative

DISCUSSION

Post-vaccine lymphadenopathy

Post-vaccine lymphadenopathy is a well-known phenomenon which may occur as a side effect of different vaccines, sometimes simulating a lymphoma, either clinically or pathologically. SARS-CoV-2 vaccines have been the first mRNA vaccines administered on large-scale [5-15, 35, 68, 73]. These vaccines base their mechanism of action on mRNA delivered into host cells, where it is translated into a protein then targeted by the immune system [2, 16, 83, 84]. The mRNA COVID-19 vaccine's high immunogenicity might explain the higher rates of LAP, reported as side effects, when compared to other vaccines [36, 80, 81]. Assessing the real incidence of C19-LAP may be difficult, in particular for the heterogeneity of the sampled vaccinated populations, the lack of systematic investigations and the selection bias. Moreover, an additional factor impacting the evaluation of the incidence of SLDI and C19-LAP is caused by the presence of patients who undergo imaging evaluation for pre-existing morbidities and for staging or follow-up of neoplastic diseases by 18F-FDG PET-CT, in which SLDI are more likely to be detected [35, 36, 53, 61, 72, 81]. The nature of the vaccine may contribute to the morphological features of post-vaccine lymphadenopathies [11-15, 19, 67, 82, 83].

Pathology of COVID-19 post-vaccine lymphadenopathy

We retrieved 55 cases of C19-LAP with histological and/or cytological control and diagnosed as reactive lymphadenopathy (28 cases) or follicular hyperplasia (13 cases) [25-27, 30-34, 41-45, 47-56, 58, 59, 61-65, 68]. Kikuchi-Fujimoto Disease was reported in 6 cases while Tintle et al. reported Langerhans cell hyperplasia [45, 47, 48, 55, 62, 63]. Patil et al. described the case of atypical follicular hyperplasia with light chain-restricted germinal centers after COVID-19 booster [68]. The pooled analysis of 54 reports showed a mean age of 47.2±13.3 years old, with 80.0% (43/54) females. Fifteen (15/54, 28%) of these patients had no prior medical history, while six patients (6/54, 11%) had prior non-neoplastic medical history, including psoriatic arthritis in Haven et al., allergic asthma in Kaya et al., steroid-dependent minimal-change renal disease in Al Soub et al., and diabetes mellitus and hypertension in Tan HM et al. [45, 49, 50, 62]. When reported, most cases of lymphadenopathy occurred on the same side of the vaccination site, with contra-laterality reported in four cases (4/54, 7%) [31, 33, 44, 47]. The most common site of lymphadenopathy was the axillary region (28/55, 51%), followed by the clavicular (13/55, 24%) and cervical regions (6/55, 11%). The most reported associated symptoms included fever, pain. The mean dimension of lymph node reported was 21.3±10.9 mm. Ultrasound features were lymph node enlargement, cortical thickening, hypoechogenic areas, lost or partially detectable hilum and ill-defined borders [77]. Cases of KFD were reported in significantly younger patients with a mean age of 26.5±10.8 than those diagnosed with reactive lymphadenopathy (52.5±14.2 years old) and follicular hyperplasia (38.8±13.5 years old). The largest dimension of lymph node did not differ significantly amongst these three diagnoses (reactive lymphadenopathy: 24.5±12.7 mm, follicular hyperplasia: 14.3±3.3 mm, KFD: 20.4±7.9 mm). In the histopathological reports of C19-LAP, a case of Langerhans cell hyperplasia and a case of atypical follicular hyperplasia with light chain-restricted germinal centers have been described. KFD has been reported in six cases [45, 47, 48, 55, 62, 63, 68].

As already postulated for some cases of autoimmune diseases, the immunologic hyperstimulation or the hyperreactivity caused by RNA vaccines might be the reason why certain patients develop marked hyperplasia of germinal centers and pseudo-clonality [85]. In 26 out of 55 cases (47,3%), patients underwent imaging study during staging of a new diagnosed neoplastic disease or during cancer follow-up. In this kind of patients, chances of detecting subclinical lymphadenopathy as an incidental finding are increased. Moreover, it's not uncommon that reactive lymphadenopathy may show pathological or suspicious features at imaging [86, 87]. Because of this, many patients undergo surgical lymph nodes excision for actionable diagnosis, raising the already high number of invasive medical procedures they have to endure, beyond the cost of the whole diagnostic process. In these cases, LN-FNAC and LN-CNB may represent the right solution. Unfortunately, LN-FNAC is not universally accepted as a diagnostic tool whereas it has been useful in evaluating malignant processes in cases in which surgical excisions were difficult to perform [25, 28, 82, 83, 88-94]. Moreover, LN-FNAC has been useful in the management

of oncological patients, through the possibility of selecting patients who will truly benefit from CNB and, eventually, surgical excision.

CONCLUSIONS

SLDI and C19-LAP have represented a diagnostic dilemma and a clinical problem, especially in oncologic patients, which have often faced an invasive diagnostic approach. Because of the difficulties related to a surgical excision during the pandemic, CNB and FNAC, especially when combined with ROSE, have represented safe, cost-effective and accurate diagnostic tools, saving many patients an unnecessary surgical excision.

Conflict of interest
The authors have no conflict of interests related to this publication.

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