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Covishield-Induced Cervical Lymphadenopathy in a Case of Latent TB Infection: A Case Report

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ABSTRACT

The Covid vaccine pandemic of 2019 saw a surge in the production and marketing of various vaccines across the world such as Pfizer-BioNTech, Moderna, Janssen and Janssen etc that were rolled out in order to boost immunity. Two of the foremost vaccines that were marketed in India were the Covaxin by Bharat Biotech, a whole virion inactivated vaccine and the Covishield, a recombinant adenovirus vector vaccine, manufactured by the Serum institute of India. The major adverse effects that were reported with these vaccines include injection site pain, fever, myalgia, nausea, diarrhoea and giddiness. Although many serious and potentially life-threatening adverse effects following immunisation (AEFIs) have been reported with mRNA vaccines, such as Guillane Barre syndrome, myocarditis, pericarditis and thrombocytopenia, no such literature exists as to the safety profile of Covishield vaccine. This report aims to discuss the incidence of a sudden-onset ipsilateral cervical lymphadenopathy in a 31 year old male health care worker, with previous history of Tb, working in a teaching hospital in India, following inoculation with the second dose of Covishield vaccine. Relevant history -taking and investigations including imaging, cytology and microbiological examination were done to establish the causality of the case and rule out other differentials, namely Tb and malignancy. This is the first such reported case of cervical adenopathy following Covishield vaccination and highlights the need for prompt adverse event reporting and management in any presentation with a neck lump.

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Key Words
Cervical lymphadenopathy, Covid-19 vaccination, latent TB infection, ultrasound, covishield

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INTRODUCTION

The coronavirus epidemic of 2019 was a global epidemic caused by the severe acute respiratory syndrome Coronavirus 2 (SARS Cov-2) that saw a series of vaccines being introduced by pharmaceutical companies in India and abroad. The two predominant vaccines that were approved and launched in India were the Covaxin, a whole virion inactivated vaccine developed by Bharat Biotech, in collaboration with the Indian Council of Medical Research and the Covishield vaccine, a recombinant adenovirus vector vaccine, developed by Oxford University/Astrazeneca and marketed by the Serum Institute of India. Covaxin was indicated for >18 years of age in two separate doses 4-6 weeks apart intramuscularly whereas Covishield was approved for >18 years of age in two separate doses 12-16 weeks apart. As of March 2023, India has rolled out over 2.2 billion doses of Covid 19 vaccines overall, including first, second and booster doses. The major adverse effects that have been reported with these vaccines included pain at the injection site, fever, fatigue, muscle ache, chills, nausea, giddiness and diarrhoea . Some lesser common side effects that were reported with mRNA vaccines in the US included severe allergic reactions such as anaphylaxis, thrombosis with thrombocytopenia after Janssen (J and J vaccines), Guillan Barre syndrome and myocarditis and pericarditis. Similar reports related to ChADOx1 nCoV corona virus vaccine have not been described yet and large Phase II/III studies are still underway. Cervical lymphadenopathy is defined as abnormality in size, consistency and number of lymph nodes of the neck enlargement of the lymph nodes of the cervical region (head and neck) which is usually >1 cm in greatest diameter. It can be attributed to various causes, such as infections such as TB, AIDS, syphilis, toxoplasmosis, malignancies, autoimmune disorders, iatrogenic and other miscellaneous acute conditions such as tonsillitis, bronchitis and viral infection[1]. Unexplained lymphadenopathy as a result of reactive hyperplasia of ipsilateral axilllary or cervical lymph node following mRNA vaccination has been described in many parts of the world[2-5], although, the same with DNA vaccines has not been reported as such. It is usually a cause of concern and should be investigated thoroughly through history-taking, imaging and cytological/histopathological examinations to rule out other underlying pathologies such as infections or malignancy. Cervical lymph node enlargement as a result of reactivation of latent infections such as tuberculosis, herpes zoster, hepatitis C and A virus, CMV, Ebstein-Barr virus infection and tumor cells have also been reported and should be taken into account when considering the differentials.

Case presentation: A 31 year old, male, HCW, working in the radiation department of a central Indian teaching hospital presented with a painless lump on the right lateral side of the neck(right parotid region), 10-15 days after being inoculated with the second dose of Covishield vaccine on September 9, 2021 (Batch no. 4121M078). It was a single, soft to firm in touch, non-tender, large (around 4×3 cm in size), palpable swelling located on right posterior triangle of the neck. There was no erythema or discharging sinus in the overlying skin. The victim is a non-smoker, non-diabetic with no known medications at the time of presentation and no history of malignancy in him or in his family (Fig. 1). There were no signs of URTI at the time of presentation. The first and booster doses of the vaccine were received 102 days prior and 182 days later, respectively, to the current status, with no events being reported. Person gives history of one episode of Covid infection in the month of July-2021, as confirmed by RTPCR report.

Significant past medical history includes childhood tuberculosis at the age of 14-15 years which was cured with antitubercular regime. There was no documentation to confirm completion of ATT course. Person is immunised with BCG vaccine at birth.

The findings prompted USG screening of the neck, done a week later on 3rd October 2021. It revealed multiple heterogenous, hypoechoic, round to ovoid structures bilaterally, in the cervical region at levels Ib, II, III, with maintained central fatty hilum and sphericity index, the largest lymph node measuring 3×2.1 cm (right-1b) noted at scan (Fig. 2). No matting of the lymph nodes or intranodal necrosis was seen. Thyroid and bilateral parotid were noted to be normal in echotexture and vascularity.

Person was asked to follow it up with USG- Guided FNAC as the gold standard procedure to rule out any metastatic or infective pathologies. USG- guided FNAC done on 6th October revealed dense neutrophilic infiltrate against dirty necrotic background suggestive of “acute suppurative lymphadenitis”. No epitheloid cell granulomas or atypical cells were noted in the

Fig. 1: Case subject. Since the picture was taken retrospectively, cervical lymphadenopathy had resolved by then

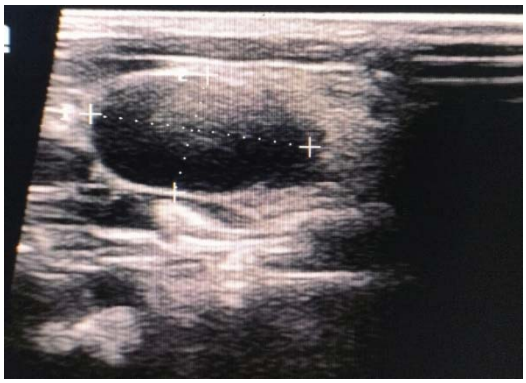

Fig. 2: USS showing, done on 3rd October 2021, shows, multiple heterogenous, hypoechoic structures, the largest being right level Ib lymphadenopathy (3×2.1 cm) with well-defined hilum and normal echogenicity and sphericity index. There is no matting of lymph nodes or intranodal necrosis seen

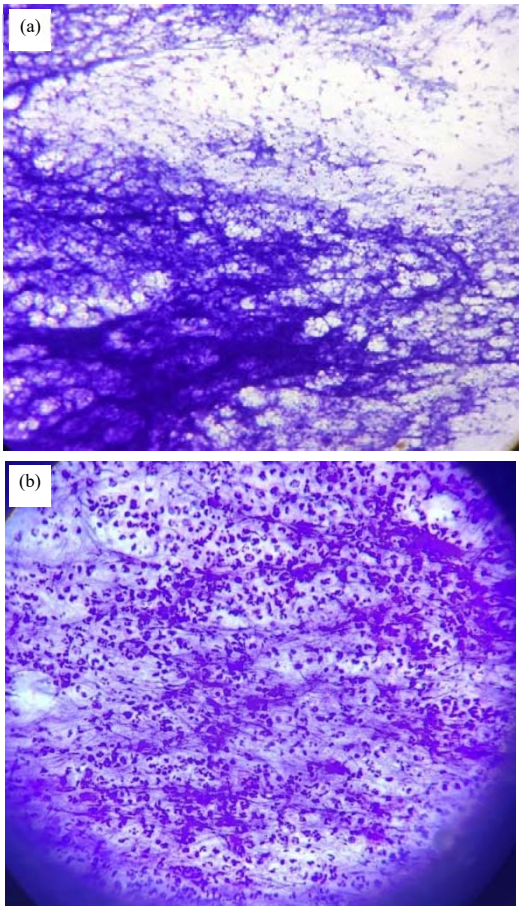

Fig. 3(a-b): H and E staining smears showing dense neutrophilic infiltrate against dirty necrotic background, without granulomas or caseation, (a) Under low resolution and (b) High resolution, respectively. Findings suggest "suppurative lymphadenitis". A: 10X; B:40X

Fig. 4: Rhodamine-auramine staining of pus aspirate, showing no evidence of acid-fast bacilli

smear (Fig. 3). There were no constitutive symptoms such as cough, night sweats, malaise or weight loss apart from occasional low-grade fever which was cured with paracetamol. Person was advised AFB, CBNAAT culture of pus aspirate and repeat FNAC after a month. Rhodamine-Auramine staining of aspirate was done following the reports of the smear (Fig. 4), followed by CBNAAT culture. There was no evidence of acid-fast bacilli in either.

Patient underwent repeat FNAC, one month later, to rule out any other pathologies. Repeat FNAC, done on 21st November, revealed necrotic and degenerated material only suggesting "necrotising lymphadenitis" as the primary diagnosis. There was no evidence of caseation or epitheloid cell granulomas. Excision lymph node biopsy was waived as there was gradual regression of symptoms without any need for intervention and also because patient was unwilling to give consent. Blood parameters were normal except for slightly raised WBC count (12,500 μL^{-1}).

However, a tuberculin skin test was performed in this patient, out of curiosity, in October, came out positive (11 mm). We proceeded to do a chest X-ray, followed by AFB sputum to rule out any possible reactivation of Tb. Chest X-ray carried out on 16 October 2021 revealed few well defined radio-opaque lesions seen in right mid and lower lung zones described as old healed calcified granulomas suggestive of old Koch's disease (Fig. 5a). There was no consolidation or cavitary lesions seen in the upper zones suggesting active tuberculosis. However, unilateral hilar lymphadenopathy was noted on the right side. Findings were corroborated by HRCT thorax, done on the same day, which revealed fibronodular opacities with calcification seen in the apical and anterior segments of right upper lobe, suggestive of healed granulomas. Calcified lymph nodes were noted in pre-tracheal, perihilar and para-aortic regions as well (Fig. 5b). Findings were suggestive of old healed Koch's

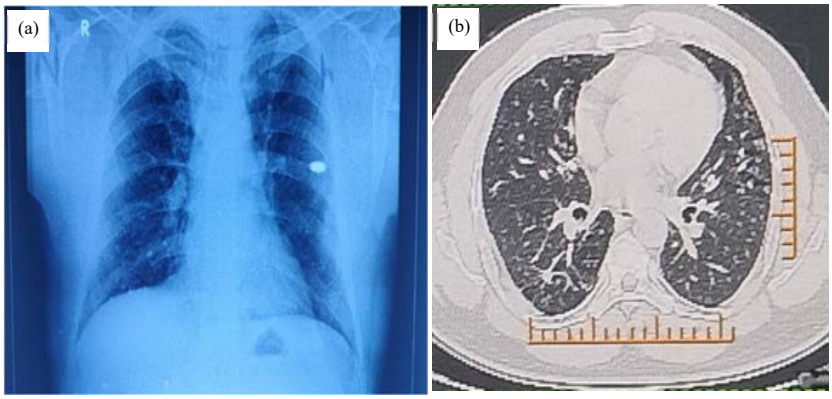

Fig. 5: (a) Chest X-ray (PA) with nodular calcifications and right hilar lymphadenopathy(in circle) and (b) HRCT thorax showing fibronodular opacities with calcified lymph nodes (arrow marks) in both lung fields s/o of healed chronic granulomatous disease

disease. AFB sputum was negative, however, IGRA test (Quanti FERON-TB Gold In-Tube test) was positive for this patient confirming latent infection.

By 40-45 days, the swelling had completety regressed in size without any burst abscess or discharging sinuses and without the need for any ATT drugs. Patient was restarted on isoniazid therapy for 6 months in view of positive tuberculin test.

The above findings clearly suggested “reactive” type of inflammatory lymphadenitis to Covid antigen followed by necrosis in post- vaccination state as the cause of lymphadenopathy.

DISCUSSIONS

The findings of the study can be summarised in two parts. In the first part, we will discuss the plausibility of lymph node enlargement following ChAdOx1 nCoV-19 viral spike protein injection into the body. Later, we will try to rule out the other possible causes of lymphadenopathy, such as extrapulmonary TB in this case, by performing relevant investigations.

The Covishield vaccine is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. It is slightly different from other mRNA vaccines in that it uses viral vector platform to inject DNA instead of mRNA into the cells to instruct them to produce antibodies and start an inflammatory cascade. The SARS-CoV-2 mRNA vaccines induce neutralizing antibodies against SARS-CoV-2 viral spike proteins that produce relatively high incidence of non serious adverse events but relatively low incidence of serious adverse event as reported in Pfizer-BioNTech and Modern vaccine trials(combined risk ratio: 1.16; 95% CI: 0.97-1.39)[6]. Serious adverse events have included stroke, MI, pulmonary embolism, myocarditis and pericarditis, venous sinus thrombosis, Bell’s palsy and intracranial haemorrhage[7]. The mechanism behind these has been explained in a review by Matsumara that showed that intramuscular administration of lipid nanoparticle (LNP)-encapsulated mRNA vaccine induces transient inflammation that mobilises neutrophils, monocytes and dendritic cells to the administration site, which then take up the LNP-mRNA and migrate to the draining lymph nodes for antigen presentation to T cells, resulting in lymphadenopathy[8]. The antigen presentation routes via MHC class II and class I induce neutralizing antibodies via Tfh cell and B cell responses and cytotoxic T-cells, respectively, that destroy the viral proteins while mounting an inflammatory response through production of cytokines (IL-1, IL-6, IFN-α, IFN-γ etc.), activated macrophages and cytolytic molecules such as perforin and granzymes that lyse infected cells and circulating pathogens[9]. This might explain local reactions such as “suppurative lymphadenitis” and systemic reactions such as fever, chills and malaise following mRNA vaccination. The same logic can be extended to DNA-based vaccines as well. Some other vaccines that have been implied in causing lymphadenopathy are human papilloma virus, BCG, measles and influenza vaccine[3]. This immunomodulated state may also be responsible for reactivation of other latent infectious conditions such as herpes zoster, CMV, Hepatitis A and C, varicella zoster, Epstein Barr virus and tuberculosis as have been reported following Covid vaccination[10-13]. Tuberculosis is the first differential when it comes to persistent cervical lymphadenopathy (>6 weeks) in endemic zones like India and should be carefully weighed through appropriate clinical investigations including chest X-ray, sputum culture and excisional biopsy of the lymph node as the gold standard to exclude TB[14].

Data from Covid 19 vaccine clinical trials suggest that the first two FDA approved Covid-19 vaccines, the Pfizer-BioNTech and the Moderna Covid - 19 vaccines, which are both based on novel mRNA technology,

as highly immunogenic, with a large number of patients reporting both local and systemic reactions[8]. Compared to this, the Covishield vaccine carries a relatively safer profile with the main adverse effects reported being injection site pain, malaise, headache, fever, fatigue and myalgia in a large multicentric phase II/III trial[15].

Data from Pfizer/BioNTech trials in the US have demonstrated a higher incidence and severity of adverse drug reactions in younger patients in the 16-55 years age group (0.5%) compared with the over 55 years' age group (0.1%). No difference as per gender was reported. Similarly, Covid-19 vaccine associated lymphadenopathy was more frequently reported in younger individuals (aged 18-64years) following the first and second doses of Moderna Vaccine (11.6 per cent and 16 per cent, respectively, compared with individuals aged 65 Years or more (6.1 and 8.4%, respectively)[16,17]. The median time to onset of such events was 2-3 days after either dose and all cases resolved within 2 weeks[16]. This was confirmed in a case series of 20 female HCW by Fernandez-Prada where full resolution of symtoms was seen within 2 weeks[2]. In our case, the subject was a 31 year old year old health care worker whose symptoms started 10-15 days after the inoculation and had fully resolved by 5-6 weeks from disease onset. Longer duration of symptoms could be attributed to his recent Covid infection or immunocompromised state. As a rule, any lymphadenopathy persisting beyond 6 weeks should be carefully monitored through invasive procedures including excisional biopsy and blood investigations including biomarkers, to rule out malignancy or other causes[1]. In this case, since the lymph gland had regressed spontaneously in size by 6 weeks, no invasive procedures were deemed necessary.

CONCLUSION

In summary, the immunogenicity and/or reactogenicity of Covid 19 mRNA vaccines are thought to be mediated by the MDA5-IFNAR1 (melanoma differentiation associated gene 5-IFN alpha and IFN-beta receptor subunit (1) Signalling pathway (Tahiteni by the encoding mRNA, lipopolysaccharide nanoparticles and/or vaccine-encoded viral spike proteins and similar explanation can be extended to DNA vaccines as well. This needs careful history-taking, monitoring and workup to rule out the differentials in any presentation with a neck lump following Covid vaccination. Also, the Covishield ChADOx1nCoV-19 is a first indigenous vaccine manufactured by the Serum Institute of India after technology transfer from Oxford/Astrazeneca, so careful monitoring of adverse effects though large multicentric trials is necessary to ensure its long term safety and efficacy. The need for fast-tracking references through dedicated pathways of emergent adverse effects post Covid-19 vaccination is to be highlighted. More such studies or systematic reviews should be conducted to confirm the findings of this report and to differentiate between safety and efficacy of mRNA versus DNA vaccines. Cervical lymphadenitis is a rare and reported adverse effect following Covid vaccinations and should be investigated through radiological imaging, FNAC and trucut biopsy to rule out other differentials.

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