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Vaccines and risk of lymphoedema

A case report of a breast cancer patient

Background

Vaccinations have been linked to lymphoedema but there is no quality scientific evidence to support or refute a causative relationship.

Objective

We report on a case of a breast cancer patient who developed lymphoedema following vaccination in her 'at risk' arm. She had previously undergone mastectomy and axillary clearance but did not have lymphoedema before the vaccinations.

Discussion

The risk of lymphoedema is still present for many years following breast surgery. Patients who are at risk of lymphoedema should be warned to report persistent swelling after vaccination so that they can be referred early for physiotherapy intervention if required.

Keywords

vaccination; adverse event; lymphoedema

vaccinations, Melba had no visible oedema and no signs or symptoms to indicate the presence of lymphoedema. She took pantoprazole for gastro-oesophageal reflux disease. There was no other significant medical or medication history.

Melba was started on cephalexin, 500 mg four times per day, to cover any possible developing infection. Over the following week, her arm oedema worsened, despite the antibiotic treatment. Melba was advised to consult her breast cancer surgeon who referred her to a lymphoedema clinic.

Melba was seen at the lymphoedema clinic 20 days after the vaccinations. Examination revealed extensive, predominantly pitting, oedema of the left forearm and upper arm, with mild oedema seen on the dorsum of the left hand. A single frequency bioimpedance analysis device was used to assess the extent of the lymphoedema (*Table 1*).¹⁻⁴ Melba's L-Dex[®] score was significantly elevated at 41.7. In addition, her left forearm circumference was 2.5 cm greater than the same reference point on her right arm. Importantly, Melba was right-handed and therefore probably had use hypertrophy of the right arm, which would have reduced the potential difference.

Melba started treatment with a physiotherapist for the lymphoedema, which included daily manual lymphatic drainage, daily multilayer bandaging from the dorsum of the hand to the upper arm and prescription of a compression garment. Two weeks later, the L-Dex[®] score was reduced to 28.0 and a marked reduction in arm oedema was observed. Melba then embarked on her South American holiday and was reassessed

Case study

Melba, 75 years of age, presented to her general practitioner with extensive left arm oedema 2 days after visiting a travel clinic for vaccinations in anticipation of travel to South America. There was no fever, pain or heat associated with the oedema. At the travel clinic she received a combined diphtheria-tetanus-acellular pertussis and inactivated poliovirus vaccine (Boostrix[®]-IPV) in her left arm at the deltoid subcutaneously, and yellow fever (live) and hepatitis A and typhoid fever vaccines in her right deltoid (intramuscularly).

Melba had a past history of a left mastectomy, axillary lymph node dissection and chest wall radiotherapy for node negative breast cancer 26 years previously. Her radiotherapy regimen was Cobalt radiotherapy given at 44 Gy over 22 fractions. She underwent a latissimus dorsi breast reconstruction a few years later. Before having the travel

Table 1. Assessment of the extent of lymphoedema using a single frequency bioimpedance analysis device¹⁻⁴

A single frequency bioimpedance analysis device can be used to quantify the extent of lymphoedema. This method measures extracellular fluid impedance in both limbs and can determine if there is a volume difference between limbs.¹⁻⁴ The difference in impedance is expressed as an impedance ratio. The device then transforms the impedance ratio into a lymphoedema index (L-Dex[®]), and the patient's L-Dex[®] score can be compared to a normal distribution of scores for a healthy population. The upper limits of this normal distribution are set at three standard deviations from the mean healthy L-Dex[®] score. Scores greater than 10 are considered abnormal and warrant investigation¹

on her return, 3 months after the initial presentation at the lymphoedema clinic. At this visit, her L-Dex[®] score was 20.6 and on circumferential measurement, there was less than 2 cm circumferential difference between both arms and no obvious oedema was seen. It is unclear whether this score had returned to her prevaccination baseline, as there was no baseline available for comparison. Melba was asymptomatic and was discharged from the clinic and advised to return for further treatment should her symptoms return. She remains asymptomatic 1 year after discharge, without the need for daily use of a compression arm sleeve.

Discussion

A literature review by the authors did not find any other reports of lymphoedema following vaccination. The Boostrix[®]-IPV product information states that in clinical trials in adults extensive swelling of the vaccinated limb was noted to be a rare (defined as between 1 in 1000 and 1 in 10 000) event.⁵ The reported incidence and prevalence of lymphoedema following breast cancer is varied due to inconsistencies in diagnosis, measurement and follow up; with overall incidence of up to 34% after surgery and radiotherapy that excludes the axilla.⁶

Eighty percent of patients with lymphoedema describe onset within the first 3 years after surgery, with the remainder developing lymphoedema at a rate of 1% per year.⁷ The National Breast and Ovarian Cancer Centre Review of Research Evidence on Secondary Lymphoedema⁸ found no evidence linking

vaccination to lymphoedema development but observed that women are often given advice to avoid vaccinations and injections in their 'at risk' arm.⁸ This advice may be based on one study that reported hospital skin punctures as a risk factor for lymphoedema in breast cancer patients.⁹ The study reported that the relative risk of lymphoedema was 2.44 for women who have had a skin puncture in the arm (n=18) compared to women who have not (n=170).⁹ However, the study's definition of skin puncture incorporated continuous infusion via cannula, venepuncture for blood tests and repeated finger prick tests (for blood glucose) and did not include vaccination. Importantly, the proposed mechanism of lymphoedema development from skin puncture is via trauma and skin infection, and not via an immunological response (as may be postulated in the case of vaccination).

The exact pathophysiology in our case study is unclear. Subcutaneous immunisations may increase the risk of lymphoedema development or exacerbation compared to intramuscular ones, perhaps due to a marked increased in dermal lymphatic flow resulting from a powerful immunogen such as Boostrix[®]-IPV.¹⁰ Importantly, the Boostrix[®]-IPV product information states that Boostrix[®]-IPV should be administered by deep intramuscular injection.⁵ In patients with a background risk of lymphoedema from surgery and/or radiotherapy for breast cancer, activated dendritic cells may then travel from the injection site through the remaining lymphatic vessels, taking up residence in residual lymph nodes and stimulating strong local vaccine specific T and B cells, but at the same time endangering previously adequate lymphatic flow. The systemic response to the live yellow fever and hepatitis A typhoid fever vaccines may have contributed to lymph

overload in the contralateral arm in this case.

In our case study, the oedema resolved with attenuation of the acute vaccine response, but this took some months. Arthus (type III hypersensitivity) reactions occur rarely after vaccinations containing tetanus or diphtheria toxoids in individuals with high levels of circulating antibodies. These antibodies form local immune complexes with the administered antigen resulting in a local vasculitis with complement activation. We do not believe that this patient had a typical Arthus reaction, as she did not describe the intense local pain and heat that typically occurs within 4–12 hours of vaccination in the setting of this type of reaction.¹¹

Furthermore, we have become aware of another woman with previously treated left breast cancer developing lymphoedema of the left arm after a tetanus booster injection in the right arm. This patient presented to our lymphoedema clinic 3 months after her vaccination for follow up only, after receiving treatment at another physiotherapy clinic. The patient observed oedema of her left arm within 6 hours of the vaccination and the oedema took 2 months to resolve. There was no infection or trauma that would explain the onset of her left arm lymphoedema. She had never had lymphoedema before the vaccination. In this patient if the mechanism was simply due to circulating immune complexes, there should have been a more intense local reaction at the injection site rather than lymphoedema of the contralateral arm.

It is not surprising that there is a paucity of studies in this area, as running a prospective, randomised controlled trial vaccinating a patient's 'at risk' arm would most likely be considered ethically unsound, or would suffer in its recruitment. The purpose of this article is to highlight the perils of subcutaneous immunisations in an at risk limb many years after cancer treatment (and perhaps even in the contralateral arm of an at risk patient as highlighted by the second case described above).

Glaxo-Smith-Kline, the manufacturers of Boostrix[®]-IPV, have been informed of this adverse event. In the future it may be necessary for vaccine product information to include a reminder to warn patients of the risk of lymphoedema, or for compression garments to be worn on the at

risk limb for a period of time after vaccination. However, given that there are no studies that prove or disprove an association between vaccination and the risk of developing or exacerbating lymphoedema, care needs to be taken in the advice that is delivered to patients by clinicians. This is also true for factors such as air travel, intravenous cannulations, blood pressure cuffs, tourniquets and prolonged exposure to heat, for which there is very little evidence to support or deny a relationship with lymphoedema.

Key points

- Risk of lymphoedema in patients who have had surgery and/or radiotherapy for breast cancer may still be present many years after treatment.
- Vaccinations may increase the risk of lymphoedema, regardless of whether or not the injection is performed on the 'at risk' side.
- Early referral to an appropriate lymphoedema physiotherapist is recommended should lymphoedema occur following vaccination.

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Conflict of interest: none declared.

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