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Development of Lobular Panniculitis Long After Completing the Personalized Peptide Vaccine Therapy

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Patient: Female, 64
Final Diagnosis: Lobular panniculitis
Symptoms: Subcutaneous indurations
Medication: —
Clinical Procedure: Skin biopsy/Administration of prednisolone
Specialty: Oncology

Objective: Patient complains/malpractice

Background: Personalized peptide vaccine therapy is regarded as a well-tolerated, safe and effective immunotherapy for patients with advanced cancers. Herein we report an exceptional case of a patient with advanced pancreatic cancer who developed delayed lobular panniculitis at sites corresponding to vaccine injections.

Case Report: A 64-year-old Japanese female visited our clinic due to thirst and polydipsia; she was diagnosed as having type 2 diabetes. Simultaneously, she was diagnosed as having advanced pancreatic cancer; and a distal pancreatectomy and splenectomy were performed. Afterwards, she received adjuvant chemotherapy with titanium silicate-1 and personalized peptide vaccination using Montanide® ISA-51 by a subcutaneous injection to her abdomen over a total of 30 times. Thirteen months after the vaccine therapy had come to an end, lobular panniculitis appeared at the vaccination sites. At this point, corticosteroid was administered, resulting in significant improvement in the condition of the subcutaneous nodules.

Conclusions: This case report highlights the importance of careful patient explanation before initiation of cancer vaccine therapy about the possibilities of lobular panniculitis as an adverse event. It also highlights that it is important that physicians have a greater awareness of the possibility of panniculitis in patients with concerns regarding subcutaneous indurations even long after the end of peptide vaccine therapy.

MeSH Keywords: Adjuvants, Immunologic • Cancer Vaccines • Drug-Related Side Effects and Adverse Reactions • Pancreatic Neoplasms • Panniculitis

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Background

In the past decade, cancer immunotherapy has rapidly progressed and is now widely used in conjunction with surgery, chemotherapy, and radiation therapy. Notably, there are many reports on the benefits of immunotherapy in the treatment of advanced cancer [1]. Dermatological reactions at the injection sites, including redness, small lumps, and ulceration have been reported as possible adverse side effects of cancer vaccine therapy. However, these symptoms are usually transient, and it is rare for them to appear in the later stages of vaccination [2]. This article describes a rare case of advanced pancreatic cancer in which the patient developed diffuse abdominal lobular panniculitis more than 1 year after completing the personalized peptide vaccines therapy.

Case Report

A 64-year-old Japanese female visited our clinic due to thirst and polydipsia in May 2011. Laboratory data showed a high blood glucose level (228 mg/dL) and hemoglobin A1c (11.6%), therefore, insulin therapy was initiated in accordance with the diagnosis of type 2 diabetes. The patient was then given an abdominal computed tomography (CT) scan, whereupon, it was suspected that she had advanced pancreatic cancer based on the elevated cancer antigen (CA) 19-9 (2640 U/mL) and the presence of low-density lesions in the pancreas with main pancreatic duct dilatation. In June 2011, a distal pancreatectomy and splenectomy were performed, and a histopathological examination showed well-to-moderately differentiated tubular adenocarcinoma in the pancreatic body with lymph node metastasis (Pb, pT3, pN3 stage IVb). Adjuvant monotherapy with titanium silicate-1 was administered and the patient was referred to the Cancer Vaccine Center in Kurume University where she received the personalized peptide vaccines therapy.

The patient was tested for human leukocyte antigen (HLA)-A and was found to express HLA-A2. Among 31 HLA class I-restricted peptide candidates, which were identified from a variety of tumor-associated antigens using tumor-infiltrating lymphocyte clones/lines, 10 peptides for HLA-A2 were selected and IgG responses specific to each vaccine peptide were analyzed in blood samples before vaccinations (Table 1). The peptides for vaccine were selected based on the titers of peptide-specific IgG titers. Four peptides (3 mg/each peptide) as 1.5 mL emulsion mixed with incomplete Freund's adjuvant (IFA) (Montanide® ISA-51, Seppic, Paris, France) were subcutaneously administered into her abdomen and the upper inner side of her thigh once a week for 6 consecutive weeks. Vaccine peptides were re-selected at every cycle and a total of 5 cycles (30 times) were administered in subcutaneous tissues between September 2011 and January 2014 (Table 1). The vaccine injection sites were changed for every session.

Beginning in March 2013, monthly systemic chemotherapy using gemcitabine (1000 mg/m^2) was administered because of the re-elevation of CA19-9 and emergence of obstructive jaundice. Thirteen months after the peptide vaccine therapy ended, the patient felt subcutaneous indurations in her right lower abdomen; over the next 3 months those indurations spread to the entire abdomen and the flank and upper inner side of the thigh at sites corresponding to vaccine injections. Upon these findings, she was admitted to our hospital on July 2015 for further examination and treatment.

Table 1. IgG responses to the vaccine peptides.

Peptide	1st	2nd	3rd	4th	5th	Post 22 months
CypB-129	ND	ND	33	23	**24**	16929
Lck-246	**36**	**28**	**365**	**11124**	10514	10276
Lck-422	ND	ND	35	**131**	**85**	ND
ppMAPkkk-432	ND	ND	ND	ND	ND	ND
WHSC2-103	**17**	**141**	**7547**	6896	6587	148
HNRPL-501	ND	ND	58	**143**	7335	16722
UBE2V-43	ND	ND	59	28	ND	ND
WHSC2-141	**29**	**16**	**1765**	**15177**	15686	8493
HNRPL-140	ND	ND	127	65	37	25229
SART3-302	**420**	**4284**	**20126**	20135	19882	19864

ND – Not determined. The peptide-specific IgG titers were determined just before each cycle. At the time point of "post 22 months" indicate 22 months after the 5th vaccination when this patient was treated with 20 mg/day prednisolone. Values indicate the peptide-specific IgG titers (Fluorescence intensity). Bold values indicate the selected peptides for corresponding vaccination.

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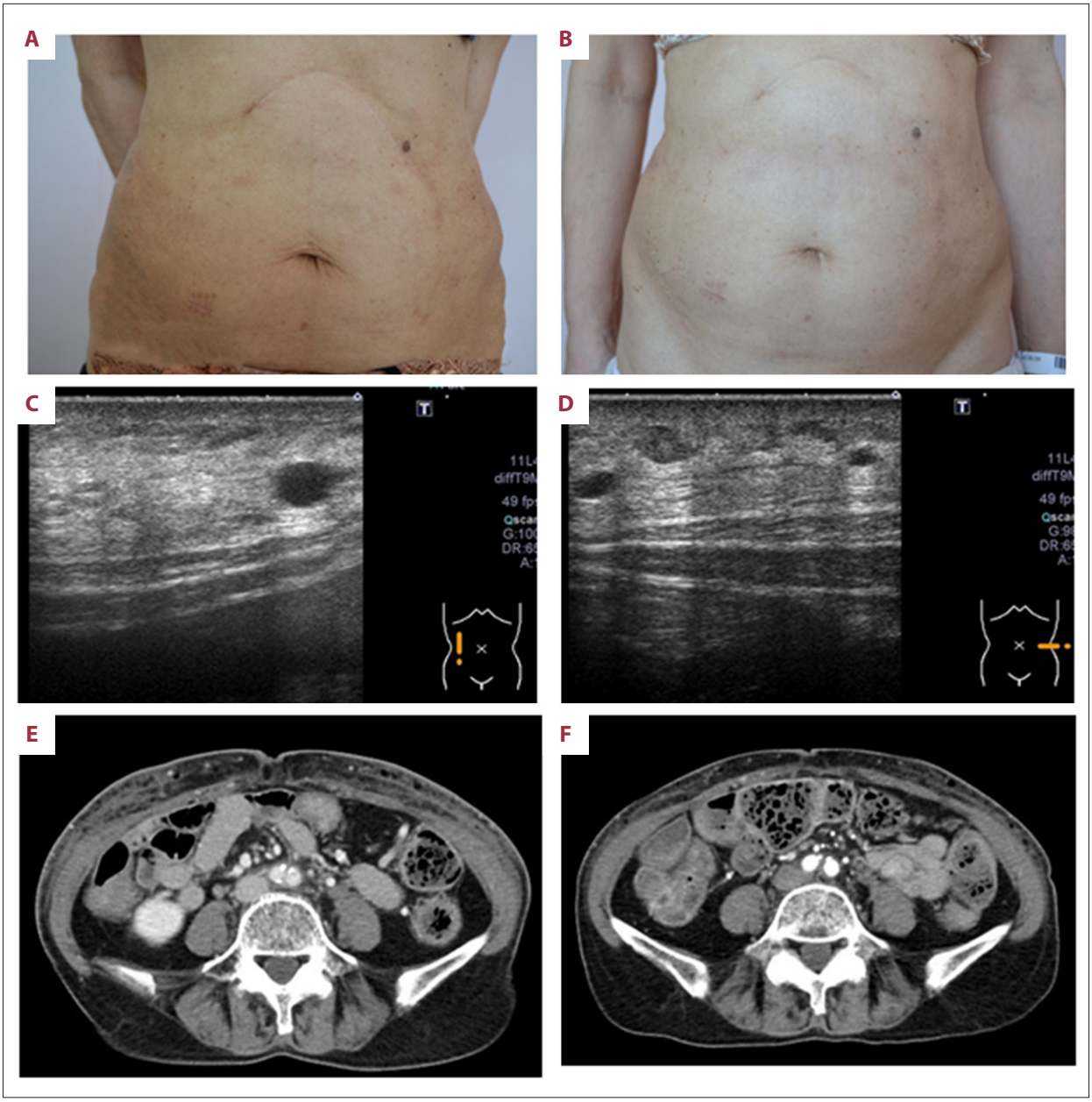

Figure 1. Photograph of the patient's abdomen and abdominal ultrasound and computed tomography (CT) scan images. Multiple subcutaneous indurations with hyperpigmentation in her abdomen can be observed at the time of admission (**A**). Photograph of the patient's abdomen 30 days after prednisolone therapy. Reduction of abdominal subcutaneous indurations as well as improvement in irregularities in the abdominal skin surface can be observed (**B**). Ultrasound of abdominal skin using a linear probe (**C, D**). CT image in transverse view obtained at the time of admission. A reticular shadow in the abdominal subcutaneous fat layer with fogging effect in the superficial fascial layer can be seen (**E**). CT image in transverse view obtained at one month after the administration of prednisolone. The abnormal findings saw undeniable improvement (**F**).

On admission, she was 142.6 cm tall and weighed 38.2 kg (body mass index 18.8 kg/m^2). A general physical examination showed no abnormalities except for the multiple subcutaneous indurations with hyperpigmentation affecting her entire abdomen and thigh (Figure 1A) at the locations where numerous peptide vaccination had been injected. With the exception of mild anemia, a routine blood examination including blood cell count, blood chemistry, and immunology showed the patient was within the normal limits (hemoglobin 10.7 g/dL). Serological tests showed a mild elevation of C-reactive protein

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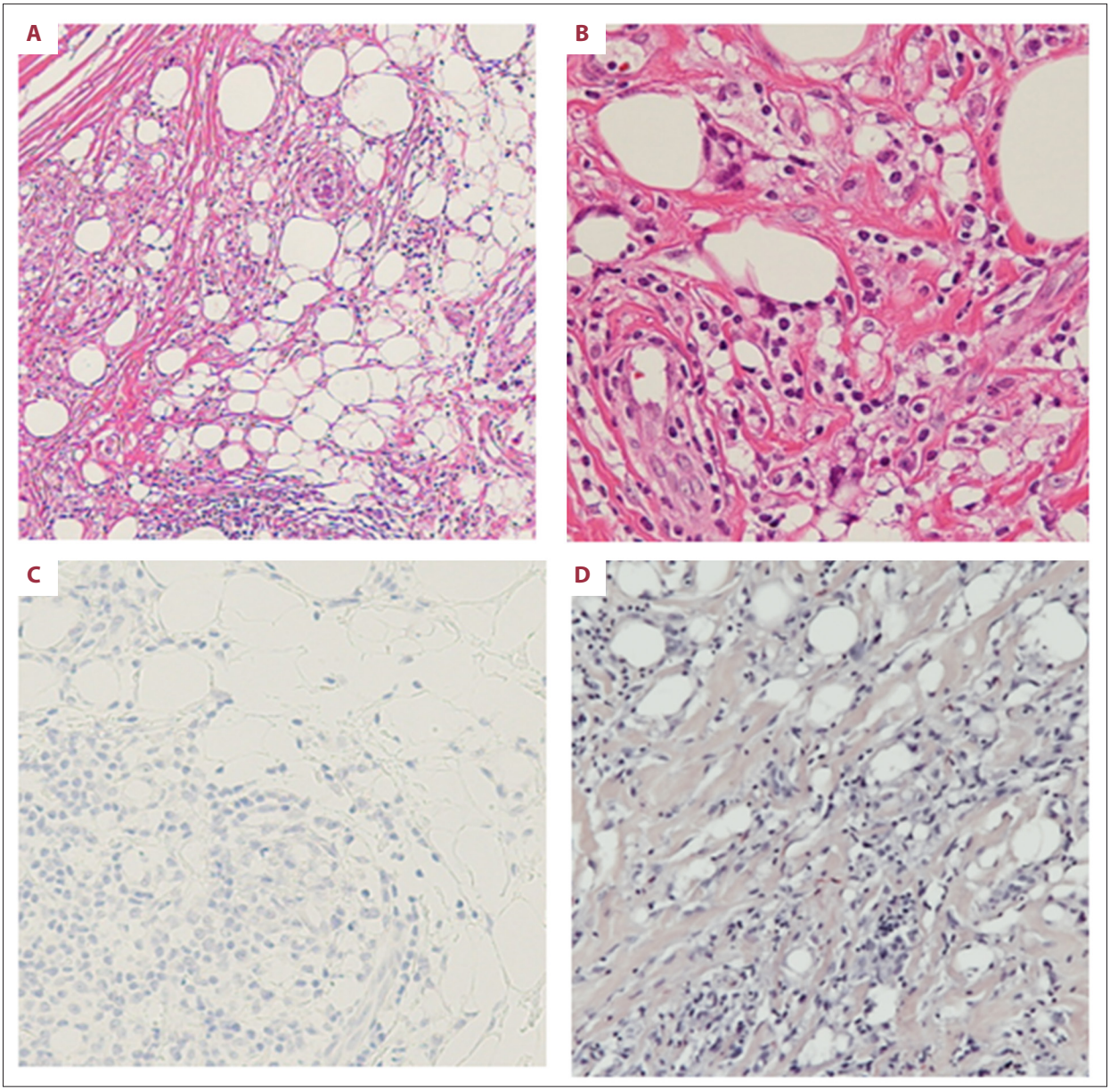

Figure 2. Histopathological examination of a skin biopsy specimen: (**A**) hematoxylin and eosin stain (magnification 200×) and (**B**) hematoxylin and eosin stain (magnification 400×). Lobular panniculitis with fat necrosis (Ghost cell) and infiltration of granulocytes, histiocytes, and multinucleated giant cells in the subcutaneous fat tissue can be observed: (**C**) amylase staining (magnification 400×) and (**D**) direct fast scarlet staining (magnification 400×).

(CRP was 0.12 mg/dL) but diabetes-related and connective tissue disease-related autoantibodies were negative. Tumor markers were as follows: carcinoembryonic antigen (CEA) 4.3 ng/mL, CA19-9 1100 U/mL, and pancreatic cancer-associated antigen-2 (DUPAN-2) 81 U/mL. An abdominal ultrasound revealed a thickening of the subcutaneous tissue and multiple subcutaneous nodules of varying size and morphology: hypoechogenic, and mixed, in part hypo-echogenic when compared to the surrounding subcutaneous fat. Hypo- or mixed-echogenic nodules with posterior acoustic shadowing had the appearance of lipid cysts (Figure 1C, 1D). A skin biopsy was performed using tissue from the nodules. A histopathological examination of the skin biopsy specimen revealed lobular panniculitis accompanied by fat necrosis, the infiltration of granulocytes, histiocytes, and multinucleated giant cells in the subcutaneous fat tissue (Figure 2A, 2B). There were no histological findings of vasculitis and amylase staining performed for differential diagnosis of pancreatic panniculitis was also negative (Figure 2C). Besides this, a direct fast scarlet (DFS) staining biopsy was performed for differential diagnosis of insulin-induced amyloidosis

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to ascertain whether or not the nodules found in the abdomen of the patient were a result of the insulin injection therapy (Figure 2D). However, the non-presence of an amyloid deposition indicated that this was not the case. In further studies, panniculitis associated with connective tissue diseases, such as Weber-Christian disease, was also ruled out, as the patient experienced neither fever nor joint pain, and was negative for both raised CRP and anti-nuclear antibodies.

Treatment with prednisolone was initiated at a dosage of 30 mg/day and gradually decreased (5 mg/week) to 10 mg/day, which resulted in the softening and reduction of abdominal subcutaneous indurations as well as causing improvement in the irregularities in the abdominal skin surface (Figure 1B). Before the administration of prednisolone, a contrasting CT scan of the abdomen showed a reticular shadow in the abdominal subcutaneous fat layer with fogging effect in the superficial fascial layer (Figure 1E). These findings were shown clear improvement at one month after the administration of prednisolone (Figure 1F).

Discussion

Cancer vaccine therapy is a type of immune-based therapy that recruits and activates the host's T-cells to target tumor-specific antigens. In treating pancreatic cancer, there are 2 major types of vaccine therapies: whole-cell vaccines and antigen-specific vaccines [3]. We utilized a novel antigen-specific vaccine approach, called "personalized peptide vaccine". Appropriate peptide antigens used in this treatment were screened and selected based on both the patient's class I HLA type and their immune response to a set of potential class I HLA-specific peptide vaccination candidates [4]. The survival period of our patient reported here has been extremely long, indicating the efficacy of personalized peptide vaccine therapy.

The vaccine antigens for personalized peptide vaccine therapy are selected based on the HLA class I phenotype and the pre-existing immunological status in each patient to induce efficient and beneficial tumor-reactive cytotoxic T lymphocytes. Peptide-based vaccines, however, need to be combined with adequate immune adjuvants, such as alum or IFA, due to either a lack of potent anti-tumor immunity or the induction of undesired immunity. In this patient's case, an IFA (Montanide ISA-51) was used as immune adjuvant. Four peptides for HLA-A2 were selected from a list of 10, based on the titers of the peptide-specific IgG before vaccination, and were subcutaneously administered as a complex with Montanide ISA-51 once a week for 6 consecutive weeks (Table 1). No adverse side effects were evident during the personalized peptide vaccine therapy, but multiple subcutaneous indurations developed at sites corresponding to vaccine injections 13 months after the peptide vaccine therapy ended.

Although the etiology of lobular panniculitis in this patient remains unclear, we strongly suspect a correlation between the vaccine therapy she received and her panniculitis because of the close relationship in the distribution of subcutaneous indurations and the vaccine therapy injection sites. It has been reported that the peptide-related adverse side effects are associated with both cellular and humoral responses specific to the vaccinated peptides and boosted immune responses were observed around the onset of vaccine-related adverse side effects [5]. Because the peptide-specific IgG titers in post-vaccination plasma increased >100-fold compared to those in pre-vaccination plasma in this patient (Table 1), there was a possibility that vaccinated peptides were associated with her panniculitis. Another possible etiology of lobular panniculitis in this patient was related to the vehicle of the vaccine. Montanide ISA-51 is a mixture of mineral oil (liquid paraffin) and water that boosts the immune response to injected antigens. Since mineral oil is a foreign substance containing straight-chain saturated hydrocarbons and humans lack the necessary enzymes to metabolize interstitial exogenous oils, a foreign body reaction to mineral oil occurs. It is possible that the multiple injections of Montanide ISA-51 in this patient induced an abnormal immune response to the mineral oil thus resulting in the lobular panniculitis.

It has been reported that the injection of liquid paraffin into the penis or breasts for cosmetic purpose might induce panniculitis in such forms as skin sclerosis, atrophy, pigmentation, or skin contraction [6–8]. Furthermore, Friedrich and Zustin reported a case of paraffinoma of lips and oral mucosa resulting from the misuse of paraffin containing oils as dermal fillers in the region of the lips and oral mucosa [9].

As for adverse side effects to cancer vaccine therapy, transient dermatological reactions at vaccine injection sites, including redness, small lumps, or ulceration, are common and expected [2]. However, there have been no reports on late adverse reactions to peptide vaccine therapy, and to the best of our knowledge, this is the first case involving an advance cancer patient who developed delayed lobular panniculitis at the vaccine injection sites. In the Cancer Vaccine Center at Kurume University, Montanide ISA-51 has been used in more than 1500 cases, but none of these cases reported the development of delayed panniculitis after completing the vaccine therapy. Interestingly, it is common for the induction of lymphocytes to occur in cases in which immunity acquired while undergoing cancer vaccine therapy has been reactivated. However, in our patient's case, pathological findings indicated the migration of histiocytes and multinucleated giant cells (Figure 2A, 2B). Therefore, the sustained immune response to a peptide or foreign substance due to frequent introduction of personalized peptide vaccine might have resulted in chronic inflammation, i.e., panniculitis, in the abdominal subcutaneous tissue at the vaccine injection sites.

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Conclusions

This paper presents a rare case of delayed lobular panniculitis occurring long after the completion of personalized peptide vaccine therapy. Physicians should be aware of the possible onset of lobular panniculitis in patients who express concerns over non-painful subcutaneous indurations even long after the completion of peptide vaccine therapy. Furthermore, this finding also highlights the importance of thoroughly explaining to patients the possibility of delayed adverse side effect, such as the potential expanse of inflammation around the injection sites, and the resulting cosmetic impediments, before the initiation of cancer vaccine therapy.

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Conflict of interests

None.

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