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Case report

Kikuchi disease: A case report about Sintilimab-induced Kikuchi histiocytic necrotizing lymphadenitis and literature review

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ABSTRACT

Immune checkpoint inhibitors have become one of the effective means of solid tumor treatment, among which anti-programmed death-1 (PD-1) antibodies are more maturely applied and can effectively inhibit tumor immune escape, thus enhancing the anti-tumor effect, but it can also lead to a series of immune-related adverse events (irAEs) in the process of clinical use. Here, we report a Patient with pancreatic solid pseudopapilloma treated with Sintilimab for the fifteenth cycles who developed chills, fever, and lymph node enlargement. Considering that the patient did not have infection, without history of autoimmune disease, we diagnosed the patient with Sintilimab-induced histiocytic necrotizing lymphadenitis (Kikuchi disease). The symptoms are alleviated after rapid use of glucocorticoids. Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis) with anti-programmed death-1 (PD-1) antibody is a rare immune-related adverse events (irAEs).

1. Introduction

With the in-depth study of tumor treatment, we found that immune checkpoint (IC) proteins act as effective suppressors of the immune system, thus leading to tumor immune escape and disease recurrence. Among which PD-1/PD-L1, CTLA-4, TIGIT, and TIM3 have got much attention [1]. Immune checkpoint inhibitors can up the survival of solid tumors, Among them, PD-1/PD-L1 inhibitors are more widely used in solid tumors. By blocking the activation and proliferation of T cells, it can restore the killing effect of the immune system on tumor cells and reduce the exhaustion of T cells [2,3]. Sintilimab is a fully human immunoglobulin G4(IgG4)-type anti-programmed cell death receptor-1 (PD-1)monoclonal antibody (PD-1), thereby blocking the interaction of PD-1 with its ligands (PD-L1 and PL-L2), and helping to recover endogenous anti-tumor T cell response [4–6]. ICIs have revolutionized the poor outcome of solid tumor therapy, and although the resulting immune-related adverse events (irAEs), such as hypophysitis, rash, myocarditis, etc, are often discussed [7], the lymphatic system diseases associated with Sintilimab are rarely discussed.

With the developed use of Sintilimab in immunotherapy, cases of Sintilimab-induced lymphatic system irAE are limited. While Sintilimab-associated lymphatic system toxicity events are rarely recognized, here we report a case due to Sintilimab-induced

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histiocytic necrotizing lymphadenitis.

2. Case presentation

On October 11, 2021, Patient in their 40s was admitted to the hospital with abdominal pain for half a month, and the blood routine showed that there was no abnormality, the tumor markers (CA199, CA125, CEA, CA153) were negative, and the enhanced MRI of the upper abdomen showed soft tissue mass in the body of the pancreas, with a size of about 46mmx32mm.DWI diffusion was limited, and the enhanced scan showed uneven delayed strengthening. There were multiple small cystic non-enhanced areas and no expansion of the pancreatic duct. Diagnostic opinion: neoplastic lesions may: pancreatic solid pseudopapilloma may, other to be excluded, please combine clinical history and other relevant examinations (Supplementary Fig. 1). Patient underwent laparoscopic pancreatic body and tail resection and splenectomy at Dazhou Central Hospital in Sichuan Province. Patient was diagnosed with a low-grade malignant solid-pseudopapillary tumor after surgery. Immunohistochemical staining showed the following: Syn part^{+}, CgA^{-}, CD56^{+}, β-catenin, CK18^{+}, CK^{-}, CK20^{-}, TTF-1^{-}, Vim^{+}, ER^{-}, CD10^{+}, ER^{-}, PR^{+}, CEA^{-}, EMA^{-}, CA19-9^{-}, S-100^{-}, CDX2^{-}, CK19^{-} (Supplementary Fig. 2(A-I)). After surgical treatment, Patient began to use sintilimab sequential treatment from 2021 to 10–20 to 2022-10-13, 200 mg IV each time, every month as a cycle, and the 15th cycle of 2022-10-13 ended. Regular re-examination, no tumor recurrence on the enhanced MRI of the upper abdomen (April 27, 2022 and October 25, 2023),and the tumor markers (CA199, CA125, CEA, CA153) were persistently negative (Supplementary Fig. 3(A-B)). On October 15, 2022, the patient developed chills and fever, with the highest temperature up to 39 °C. He complained of fever at night. After symptomatic treatment with ibuprofen, he did not get well,and suddenly found bilateral submandibular and cervical lymph node enlargement with local fusion, and right lymph node tenderness. He was admitted to the Department of Hematology on October 26, 2022. Physical examination showed partial adhesion of several swollen lymph nodes in the bilateral submandibular, neck, and armpits. The largest lymph node was located in the left neck, with a diameter of about 1.5 cm. It was tough, with mild tenderness, and activity. There was no swelling, ulceration, sinus tract, etc. The remaining superficial lymph nodes did not touch the swelling. Repeatedly asked about the medical history, no such symptoms occurred at the initial stage of sintilimab treatment and before this medical history.

After admission, the relevant auxiliary examinations were completed, C-reactive protein, antinuclear antibody spectrum, EBV virus DNA, and cytomegalovirus DNA were negative, and the TSPOT test was negative (Supplementary Table 1). Lymph node color Doppler ultrasound showed multiple lymph nodes echoes in the bilateral neck, cortical thickening, and some cortical and medullary structures were blurred. The left side was larger about 28.7mmx6.8mm, and the right side was larger about 23.0mmx9.9mm.CDFI: rich blood flow signals in lymph nodes; multiple lymph node echoes were seen in the bilateral axilla and groin, and the cortex and medulla were normal, suggesting that bilateral cervical lymph nodes grew up (slightly abnormal structure) (Fig. 1).

Subsequently, we performed a biopsy of the right cervical lymph node at the Department of General Surgery of Dazhou Central Hospital and sent it to the Jinyu Detection Agency for pathological diagnosis: lymph node reactive hyperplasia, consistent with histiocytic necrotizing lymphadenitis (Kikuchi disease), please consider it together with clinical considerations. Immunohistochemical results: proliferating lymphoid tissue around the necrotic area CD3 (+), CD4 fraction (+),Ki-67 (+, about 40 % in the necrotic area and about 10 % in the rest), CD123 clustered or scattered (+); B lymphocytes CD20 (−), CD30 scattered in single transformed large cells (+)), CD68 histiocytes (+), MPO granulocytes (+), CD10 (−), BCL-6 scattered in few (+), BCL-2 (+), CylinD1 (−). (Fig. 2(A-C), Fig. 3 (A-I))

According to the above pathological test results, we consider the disease to be consistent with histiocytic proliferative necrotizing lymphadenitis. During admission to the return of lymph node biopsy results, we gave ibuprofen to relieve fever and relieve pain, and empirical levofloxacin injection to resist infection (October 26 to November 01, 2022). However, the patient still had fever and no

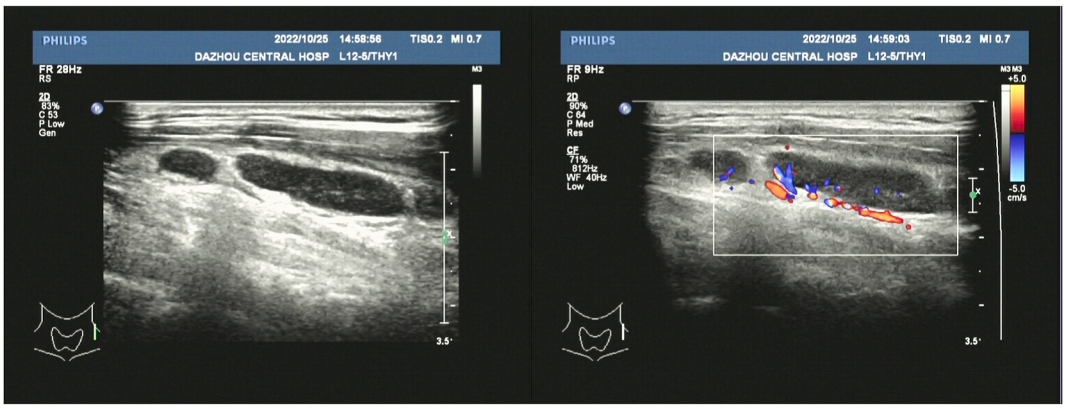

Fig. 1. Cervical lymph node color ultrasound before treatment (left). Lymph node ultrasound can be seen in bilateral neck echoes of multiple lymph nodes, cortical thickening, part of the cortical medulla structure is blurred, the left side is about 28.7mmx6.8mm, the right side is about 23.0mmx9.9mm, CDFI: the blood flow signal in the lymph node is abundant; Ultrasound: bilateral cervical lymph node enlargement (slightly structurally abnormal).

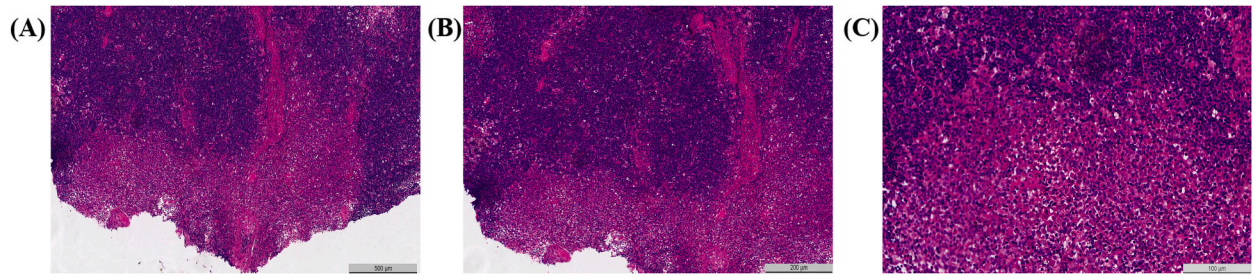

Fig. 2. HE staining of left cervical lymph nodes. (A–C) Lymph node structure disorder with necrosis, visible nuclear fragmentation. (A) Left cervical lymph node (hematoxylin–eosin, 4 × 10, bar 500 μm). (B) Left cervical lymph node (hematoxylin–eosin, 10 × 10, bar 200 μm). (C) Left cervical lymph node (hematoxylin–eosin, 20 × 10, bar 100 μm).

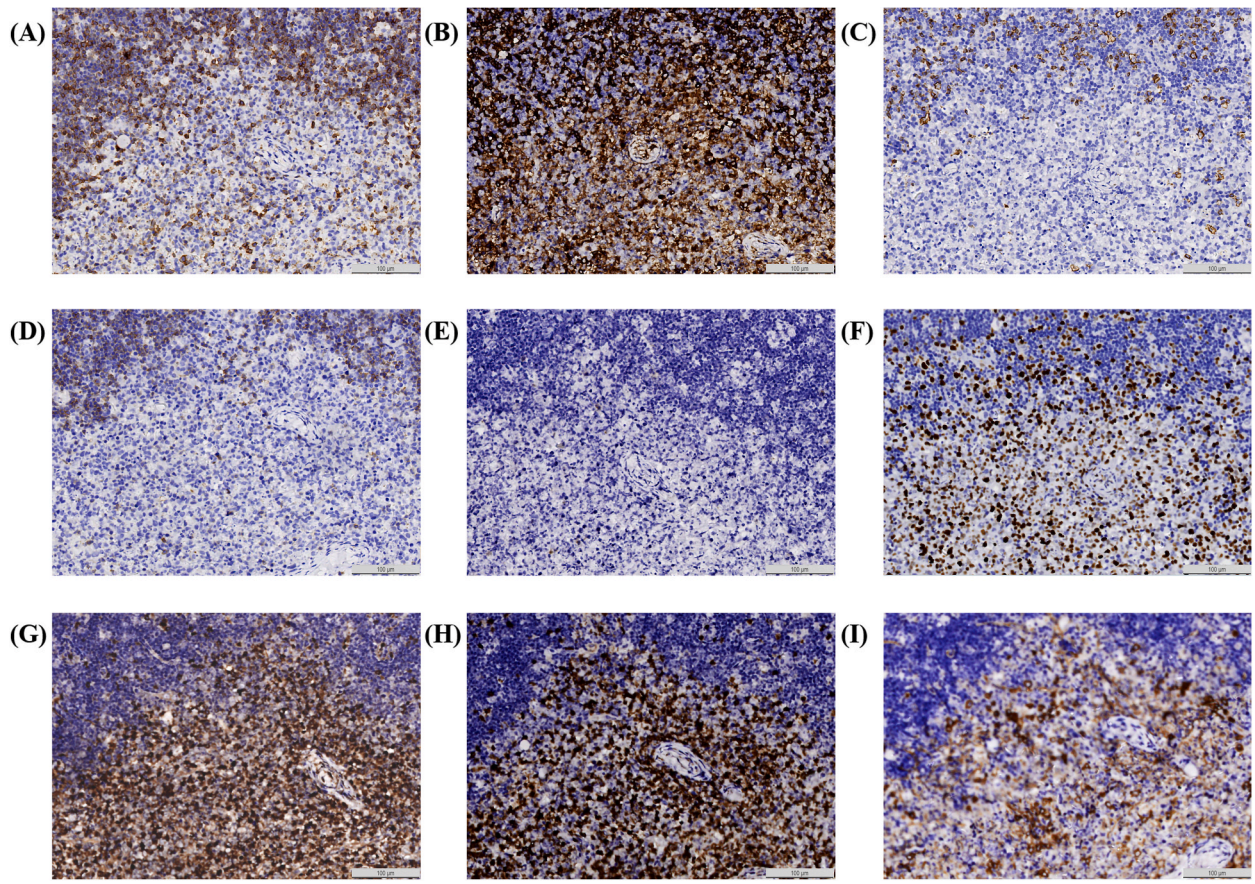

Fig. 3. Immunohistochemistry of left cervical lymph nodes. (A–I) Immunostaining shows mainly CD3-positive (A), CD4^{-}partial positive (B), CD20-negative (C), CD5-positive cells(D), CD30-positive with scattered in single transformed large cells (E), Ki-67- positive (F), CD68-positive (G), MPO-positive (H) and CD123-positive with clustered or scattered (I) (20 × 10, bar 100 μm).

obvious changes in lymph nodes. The patient and his family expressed anxiety. Therefore, immediately after diagnosis, intravenous immunoglobulin 5g × 3 days ivgtt qd was given to regulate immunotherapy, oral prednisone acetate 10mg immunosuppressive therapy, and discontinued the use of sintilimab. After treatment, the patient's body temperature was normal, no fever, and the cervical lymph nodes were significantly smaller than before. The color Doppler ultrasound of cervical lymph nodes on 2023-01-12 suggested that there was no obvious abnormal lymph node echo in the neck. (Fig. 4) (Supplementary Table 2).

3. Discussion

With the advent of the era of precision therapy and the deepening of research on tumor treatment, it has been discovered that

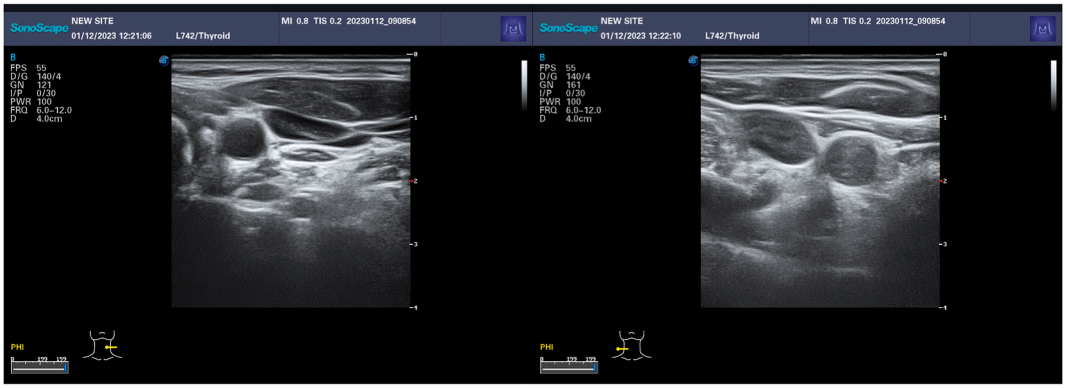

Fig. 4. Cervical lymph node color ultrasound after treatment. Bilateral neck scan: no apparent abnormal lymph node echo, CDFI: no abnormal blood flow signal.

immune checkpoint (IC) proteins as an effective inhibitors of the immune system, leading to tumor immune escape and disease recurrence [8]. PD-1, also known as programmed death receptor 1, is the most common immune checkpoint of T cells found so far. After binding to PD-L1, PD-1 down-regulates the immune system's response to human cells and inhibits T-cell inflammatory activity to regulate the immune system. During the process of tumor cell therapy, tumor cells express PD-L1 ligands and bind to PD-1 on the surface of T cells, thereby inhibiting the killing effect of T cells on tumor cells [9]. As more and more studies have found that the expression of PD-L1 is correlated with the prognosis of tumors [10]. Therefore, as one of the important immune checkpoints, PD-1 has been widely applied in clinical practice.

Immune checkpoint inhibitors (ICIs) have been widely used in the treatment of solid tumors, and immune-related adverse events (irAEs) have become new clinical challenges [11]. Sintilimab, an anti-PD-1/PD-L1 antibody approved for use in 2018, is indicated for the treatment of relapsed or refractory classical Hodgkin's lymphoma following at least second-line systemic therapy [4,12]. There are also many reports on the use of in pancreatic malignant tumors, and it also shows a certain effect [13],but has shown almost no efficacy in the treatment of pancreatic ductal adenocarcinoma (PDAC) [14].

Pancreatic cancer includes resectable, borderline resectable and locally advanced (unresectable) diseases. At the time of diagnosis, about 50 % of patients have metastasis, 10 %–15 % of patients have operable localized diseases, and the rest (30 %–35 %) [15]. For borderline resectable pancreatic cancer, adjuvant chemotherapy reduces the incidence of lymph node metastasis and local recurrence [16–18]. For terminal patient cannot receive surgical resection, or postoperative recurrence [19,20]. Chemotherapy is still the main method for advanced pancreatic cancer and postoperative adjuvant therapy. At present, the first-line treatment for most patients with metastatic pancreatic adenocarcinoma is the FOLFIRINOX regimen: oxaliplatin + irinotecan + leucovorin (LV) + 5-fluorouracil (5-FU) or gemcitabine combined with albumin-bound paclitaxel (GnP). The phase III randomized controlled study (Prodige 4/ACCORD 11) confirmed that the efficacy of the FOLFIRINOX regimen in the first-line treatment of metastatic PDAC was significantly better than that of gemcitabine monotherapy. The median OS (11.1 months vs 6.8 months, $P < 0.001$) and objective response rate (ORR) (32 % vs 11.3 %, $P < 0.001$) were significantly improved [21]. However, the efficacy of FOLFIRINOX is still limited. With the widespread use of precision and molecular therapies in solid tumors, various molecular targeted drugs, such as Larotrectinib or Entrectinib for NTRK fusion gene mutations, and Erlotinib for EGFR gene mutations, have been evaluated in pancreatic cancer. A study has reported a modest absolute benefit of only two weeks in overall survival with the combination of gemcitabine and Erlotinib [22]. In summary, the current status of molecularly targeted therapies for advanced PDAC is not satisfactory.

With the rise of immunotherapy, the progress of immunotherapy for pancreatic ductal adenocarcinoma (PDAC) is extremely difficult. Studies have shown that increased expression of PD-1/PD-L1 is associated with poor prognosis of pancreatic cancer. But PDAC is not sensitive to ICIs monotherapy [23,24]. However, there have been several attempts at clinical treatment. The Julien Taïeb team retrospectively collected the data of advanced PDAC patients with high microsatellite instability (MSI) or mismatch repair defect (dMMR) who received the combination of nivolumab and ipilimumab in 16 centers. They found that PD-1/PD-L1 inhibitors was effective and well-tolerated in MSI/dMMR advanced PDAC patients, with a median follow-up time of 18 months and a median progression-free survival time of 26.7 months [25]. In a mouse model of tongue cancer after surgery, PD1 inhibitors can delay the regeneration of tumor cells [26], and after radical resection of esophageal cancer and high-risk metastatic melanoma, adjuvant chemotherapy with PD-1 inhibitors showed disease-free survival benefits [27,28]. However, in the postoperative adjuvant drug therapy of pancreatic cancer, PD-1/PD-L1 inhibitors have not been published.

In this case, the patient 's pathological results suggest a low-grade malignant solid-pseudopapillary neoplasm (Solid Pseudopapillary Neoplasm of the Pancreas SPN), which is a rare pancreatic tumor. Surgical resection is the preferred treatment. The prognosis is good, but there is still a recurrence and metastasis rate of 2 %–10 % [29]. Among them, cellular atypia, infiltration of pancreatic parenchyma and surrounding tissues, peripancreatic vascular invasion, and peripheral nerve infiltration are highly invasive pathological manifestations of SPN, and a number of studies have found that SPN has calcifications on imaging, lesions greater than 5 cm, incomplete tumor capsule, microvascular invasion, preoperative metastasis, non-radical resection, and high proliferation index. It may be a high risk factor for recurrence, but there is still no consistent conclusion on the risk factors related to postoperative recurrence and

poor prognosis, and there is no evidence that postoperative adjuvant chemotherapy has a positive impact on the prognosis of SPN [30,31,32]. Because the clinical cases of invasive SPN are very rare, it is difficult to summarize and clarify the natural course of invasive SPN in clinical situations, which makes it difficult for clinicians or surgeons to provide patients and their families with information about invasive pancreatic SPN [33].

In this patient, there were scattered swollen lymph nodes under the pancreas during the operation. Postoperative pathology showed a slightly hard mass of grayish-white nature, about 5 × 3 × 2cm in size, which was considered to have the possibility of recurrence. Therefore, it is recommended to use 5FU-based chemotherapy alone or in combination with cisplatin [34]. After full understanding, the patient refused; subsequently, it is recommended to improve the detection of tumor genes. Due to economic reasons, it has not been successfully completed. Based on the current full understanding of PD1/PD-L1, PD-L1 is expressed in various types of tumors. Blocking the activity of PD-1/PD-L1 has therapeutic significance [35]. Studies have reported that although PD-L1 expression is negative in lung cancer, treatment with PD-1/PD-L1 inhibitors can still benefit [36]. Communication with patients can be considered to be PD-1 inhibitor Sindilimab for postoperative consolidation therapy, patients and their families agree.

However, compared with traditional cytotoxic chemotherapy, they have certain side effects, which are called immune-related adverse events (irAEs). IrAEs can affect almost any organ in the body, including the skin and appendages (20 cases, 26.7 %), endocrine system (11 cases, 14.7 %), digestive system (10 cases, 13.3 %), and others [37]. We reviewed the case reports of irAEs caused by Sintilimab, as shown in Supplementary Table 3. After the above review, we found that histiocytic proliferative necrotizing lymphadenitis (Kikuchi lymphadenitis) caused by Sintilimab is relatively rare and has not been reported, but other immune-related adverse events ($\leq$1 %) of anti-PD-1/PD-L1 antibodies have been reported [38].

Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis) is a rare disease, also known as Kikuchi disease. It is characterized by subacute necrotizing lymphadenopathy, often accompanied by fever, and the etiology is unclear [39]. Because of its lack of typical clinical manifestations, it is often misdiagnosed. The cause is unclear, but there are two broad theories - infection and autoimmune diseases. Many infectious factors such as viruses and bacteria are considered to be predisposing factors [40]. However, it is non-suppurative inflammation, ineffective antibiotic treatment and self-limited, suggesting that the disease may be related to acute viral infection. We tested negative inflammatory markers (White blood cell count,C-reactive protein, erythrocyte sedimentation rate), EBV virus, CMV virus, TSPOT, etc., no evidence of virus infection was found. So we no longer considered infection-induced during treatment.

It has been reported in the literature that histiocytic proliferative necrotizing lymphadenitis is associated with many autoimmune diseases, such as systemic lupus erythematosus, Sjogren's syndrome, Still's disease and others [41]. Among these diseases, systemic lupus erythematosus has the greatest relationship with it. Kikuchi disease has been described as a self-limiting systemic lupus erythematosus-like autoimmune disease with similar histological and epidemiological characteristics [42]. The histology of lymphadenitis in systemic lupus erythematosus (SLE) may be similar to that of Kikuchi vine disease, but the presence of hematoxylin in SLE lymphadenitis helps to distinguish it from Kikuchi vine disease [43]. However, the patient 's pathological tissue HE staining showed no hematoxylin. The patient was a woman of childbearing age and had a high incidence of autoimmune diseases. After admission, we gave the patient a complete antinuclear antibody, anti-double-stranded DNA antibody, anti-Sm antibody, anti-SSA/SSB antibody, etc., suggesting negative. The negative ANA test cannot rule out the diagnosis of SLE, but anti-dsDNA antibody and anti-SM antibody have high specificity [44]. The diagnosis of SLE is based on the 2019 EULAR/ACR SLE classification criteria. The standard includes 1 entering standard, 10 aspects and 18 standards. Each standard needs to exclude infection, malignant tumor, drug and other causes. Those who have previously met a certain standard can also be scored. The highest weight score in each aspect is included in the total score, and the total score $\geq$10 can be diagnosed [45]. This patient does not fit the criteria,so we temporarily excluded the Jaffa disease caused by autoimmune diseases.

Kikuchi lymphadenitis still needs to be differentiated from lymphoma. A study found that about 1/3 of the cases of Kikuchi disease were misdiagnosed as lymphoma [46]. It has been reported that CD123 positive is a significant feature of Kikuchi lymphadenitis [47]. Patchy necrosis and mixed hyperplasia of T and B cells, large number of reactive histocytes and a lack of Reed-Sternberg cells, which is an important pathological feature that distinguishes NHL. CD20 is negative in immunohistochemistry, also excluding the possibility of lymphoma. CD68 is positive, indicating that they have histocyte characteristics [48]. CD30 scattered in single transformed large cells (+) is considered to be reactive activated lymphocytes. According to IHC, this patient isn't lymphoma.

In view of the fact that the patient has no infection and autoimmune diseases, and has been treated with 15 cycles of Sintilimab (a total of 3000mg), we suspect that histiocytic proliferative necrotizing lymphadenitis is related to the treatment of Sintilimab. Therefore, it is recommended that the patient stop ICI treatment and start hormone therapy [49,50]. The patient showed a good response to prednisolone acetate. After treatment, the patient's body temperature was normal, no fever occurred again, and the cervical lymph nodes were significantly smaller than before. The color Doppler ultrasound of the cervical lymph nodes on January 12, 2023, showed that there was no obvious abnormal lymph node echo in the bilateral neck. Therefore, we believe that histiocytic proliferative necrotizing lymphadenitis is related to the use of Sintilimab. The patient was very cooperative and understanding of the treatment plan, and the symptoms were quickly relieved. Patients expressed gratitude and said that the use of Sintilimab was concerned about its rare adverse effects.

This case suggests that attention should be paid to the occurrence of irAE in the clinical application of Sintilimab. When the symptoms are serious, the drug should be discontinued as soon as possible and glucocorticoid treatment should be given in time. At present, there is no description of histiocytic proliferative necrotizing lymphadenitis after the use of sintilimab. Therefore, we believe that the report of this case provides a reference for ICI-related Kikuchi disease and has guiding significance for the use of Sintilimab. Of course, this study has some limitations: (1) In this case, the pathological results of the patient's pancreatic tumor suggested a low-grade malignant solid-pseudopapillary tumor, which was surgically removed, and the patient continued to receive Sintilimab monoclonal

antibody treatment. Currently, the use of Sintilimab monoclonal antibody has not been approved for the treatment of pancreatic cancer, which may be an overindication. (2) It has been reported that cytokines may be involved in the pathophysiological process of immune-related adverse events, such as interleukin-17 and interleukin-6 [51]. In this study, we did not perform related cytokine testing.

4. Conclusion

In summary, early detection, early diagnosis, and early treatment are essential for irAE to avoid related complications. Early diagnosis and early discontinuation of drug-induced diseases and the use of immunosuppressive agents (such as glucocorticoids) are beneficial to patients. This case report is instructive for the clinical adverse effects of sintilimab. This case report will help to understand the occurrence of ICI-related Kikuchi disease and has guiding significance for the use of Sintilimab in the later stage.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Our study with associated data hasn't been deposited into a publicly available repository.

CRediT authorship contribution statement

Chunxiao Ren: Writing – review & editing, Writing – original draft. **Yuqun Wang:** Writing – review & editing. **Xin Yang:** Resources. **Yinglan Tuo:** Resources. **Yaqiong Li:** Writing – review & editing. **Jichang Gong:** Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30608.

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