THERAPEUTIC ADVANCES in
Rare Disease

Case Report

A multidisciplinary approach to treating a unique case of recurrent metastatic thymic carcinoma: case report

Ther Adv Rare Dis

2023, Vol. 4: 1–9

DOI: 10.1177/26330040231190661

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***Abstract*:** Thymic carcinoma (TC) is a rare and aggressive malignancy of the thymus associated with less than 25% 5 years survivability. Our case report showcases the successful treatment of advanced metastatic TC using a multidisciplinary approach and the utility of checkpoint inhibitors in treatment of recurrent TC. A 50-year-old man presented with Raynaud's phenomenon and was found to have a stage IVb TC (T3N2M0). Eight months after management with neoadjuvant chemotherapy, surgical resection and adjuvant chemoradiotherapy, patient was diagnosed with metastasis of TC to the liver and a concurrent stage III (T2N1M0) primary sigmoid colon adenocarcinoma. Following complete resection of the colon adenocarcinoma, the patient started palliative-intent treatment for TC with pembrolizumab given PD-L1 tumor proportionate score of 100%. This resulted in a sustained complete response for 38 months. Our patient did have immune-related adverse events involving multiple organs but was able to continue pembrolizumab for a standard treatment duration of 2 years with multidisciplinary care. When recurrent disease was noted in a portocaval lymph node, pembrolizumab was reinitiated and a second complete response was achieved. The patient has maintained that complete response while maintaining an acceptable quality of life, showing that treatment with pembrolizumab is effective in patients after discontinuation with prior immunotherapy.

Plain language summary

Fighting Thymic Carcinoma: A Story of Immunotherapy and Multidisciplinary Care Triumph

The thymus is a gland located in the chest that plays a major role in the immune system, particularly before adulthood. Thymic carcinoma (TC) is a type of cancer affecting the thymus that is often challenging to treat given its inadequate response to chemotherapy and tendency to spread to other organs. A 50-year-old man was found to have advanced stage thymic carcinoma, which is associated with a less than 25% 5-year survival rate. Eight months after completing a rigorous treatment protocol of chemotherapy, surgery and radiation therapy, his original thymic cancer was found to have metastasized to the liver. Simultaneously, he was diagnosed with stage III sigmoid colon cancer. He underwent curative surgery for colon cancer and was started on pembrolizumab for thymic cancer. Pembrolizumab is an immunotherapy drug that boosts the body's own immune system to fight against the cancer. Inadvertently, it can turn immune cells against healthy tissues, which results in symptoms called immune-related adverse events (irAEs). Indeed, he experienced various irAEs involving multiple organs. These events were effectively managed by involving multiple specialists and initiating medications to calm the immune system and allow him to continue immunotherapy. He had a complete

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response to treatment and was able to complete the standard treatment course of two years. He retained a complete response for over three years before his tumor recurred. He was restarted on pembrolizumab and achieved a complete response again. This case highlights a unique presentation of metastatic TC and the utility of a multidisciplinary approach for treatment to maintain a high quality of life five years after diagnosis.

Keywords: anti-PD1 inhibitors, case report, extrathymic malignancy, immune checkpoint inhibitors, pembrolizumab, Raynaud's phenomenon, thymic carcinoma

Received: 5 February 2023; revised manuscript accepted: 6 July 2023.

Introduction

Thymic carcinoma (TC) is a rare thymic epithelial tumor (TET) lacking standardized treatment protocols due to the rarity of the disease. TC often has a poorer prognosis than thymoma, given its more advanced stage at presentation and lower likelihood for complete resection.[1] Thymomas are associated with paraneoplastic syndromes (PNS) or extrathymic malignancies (EM),[2,3] though the same association has not been noted with TC. We report a unique case of recurrent metastatic TC with concomitant Raynaud's phenomenon and sigmoid colon adenocarcinoma and its subsequent management with the immune checkpoint inhibitor pembrolizumab through a multidisciplinary approach to achieve 5-year survival while maintaining quality of life.

Case report

A 50-year-old male with no significant medical history presented with a 1-year history of myalgias and cold-induced discoloration of the fingers, typical for Raynaud's phenomenon. A subsequent evaluation revealed a 6.6 cm anterior mediastinal mass [Figure 1(a) and (b)], consistent with stage IVB (T3N2M0) poorly differentiated TC with squamous features (Figure 2). No signs of extrathoracic metastasis were noted on positron emission tomography–CT (PET-CT). Given the tumor's positioning around the left brachiocephalic vein, carotid artery and pulmonary artery, induction chemotherapy consisting of three cycles of cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 were administered every 3 weeks. The patient had a partial response to treatment and subsequently underwent sternotomy and radical resection with negative margins. Surgical pathology showed poorly differentiated carcinoma with squamous features in a background of treatment effect changes and involvement of pleura, five lymph nodes (LNs) (2/3 left hilar LNs, 3/8 thymic LNs), and lymphovascular invasion. Comprehensive next-generation sequencing of the tumor did not identify any disease-associated mutations. PD-L1 tumor proportion score was 100%, tumor mutational burden was 0 Muts/Mb, and there was no microsatellite instability. Two additional cycles of the same cisplatin/docetaxel regimen were completed as adjuvant chemotherapy, as well as intensity-modulated radiation therapy totaling 54 Gy in 27 fractions. The treatment was well tolerated, and interestingly, his Raynaud's phenomenon improved throughout his treatment course.

Intermittently, he developed acute coronary syndrome of unclear etiology requiring stent placement in the left anterior descending artery. For 8 months, the patient had no evidence of disease on surveillance imaging until chest computed tomography showed a new hepatic lesion. Magnetic resonance imaging revealed two lesions in the liver: a 1.4×1.3 cm mass in segment 5 and 0.7×0.7 cm mass in the caudate lobe [Figure 1(c)]. PET-CT scan showed new uptake in the liver and sigmoid colon [Figure 1(d) and (e)]. A biopsy of the liver lesion showed poorly differentiated carcinoma consistent with his primary TC. A colonoscopy revealed a $1.2 \times 1.1 \times 0.3$ cm lesion positive for invasive moderately differentiated adenocarcinoma (T2N1M0) in the background of tubular adenoma with high grade dysplasia in the sigmoid colon. While awaiting curative surgery of that tumor, pembrolizumab (200 mg IV infusion every 3 weeks) was initiated as the systemic agent for treatment of the metastatic TC given a PD-L1 tumor proportionate score of 100% and emerging data about role for checkpoint inhibitors in thymic malignancies.[4–7] After several multidisciplinary discussions at tumor boards, patient underwent

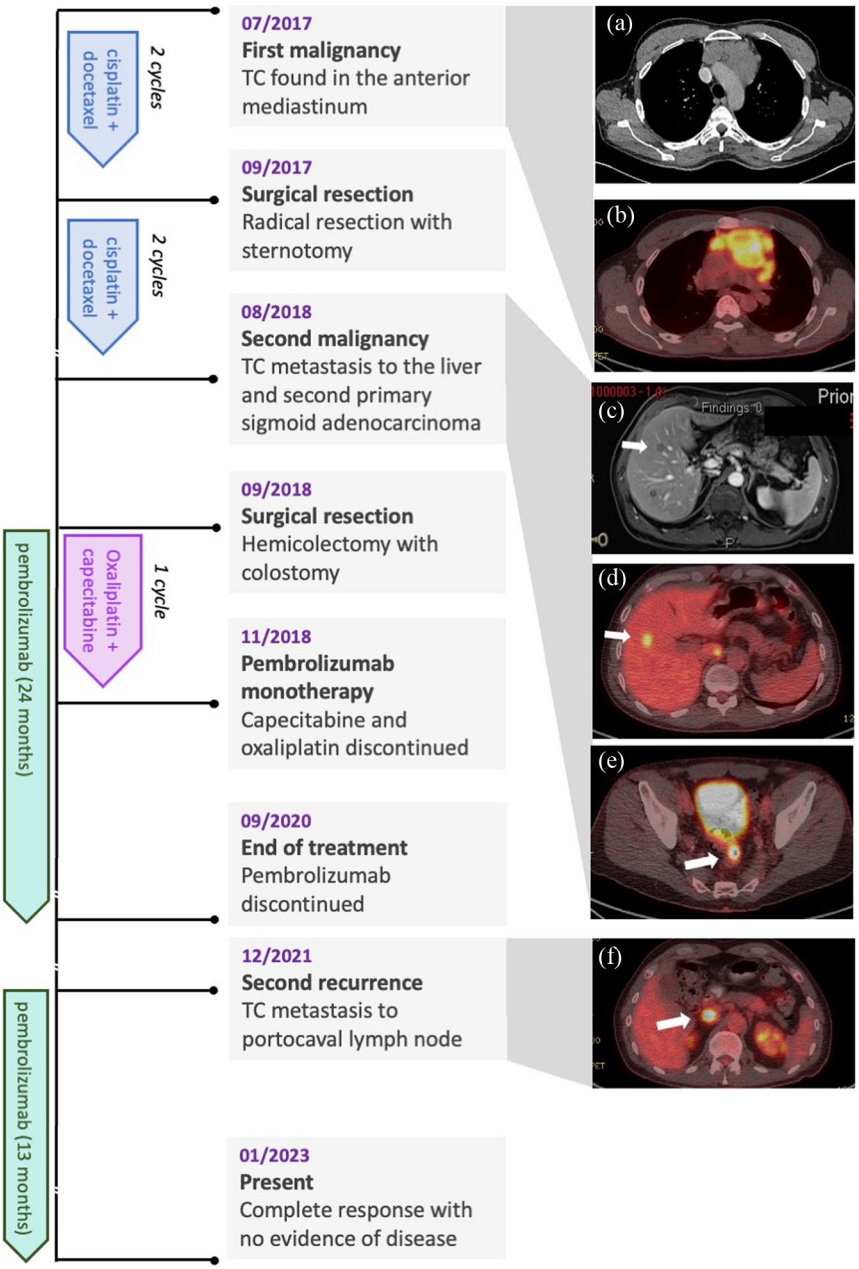

Figure 1. Timeline schematic of the patient's disease course. CT (a) and PET-CT (b) scan showing initial anterior mediastinal mass in 2017. Abdominal MRI (c) and PET-CT scan (d) showing metastatic lesion in the liver. Pelvic MRI (e) showing uptake in the sigmoid colon. (f) PET-CT scan showing metastatic lesion in a portocaval lymph node.
CT, computed tomography; PET-CT, positron emission tomography–computed tomography; MRI, magnetic resonance imaging.

hemicolectomy and was initiated on adjuvant regimen of oxaliplatin 130 mg/m^2 and capecitabine 850 mg/m^2 due to its 3 weeks cycling concordant with that of pembrolizumab. Unfortunately, this regimen had to be discontinued after 14 days because the patient developed critical coronary vascular spasm thought to be provoked by capecitabine. Our patient remained on surveillance for his colorectal cancer while continuing pembrolizumab as monotherapy for TC.

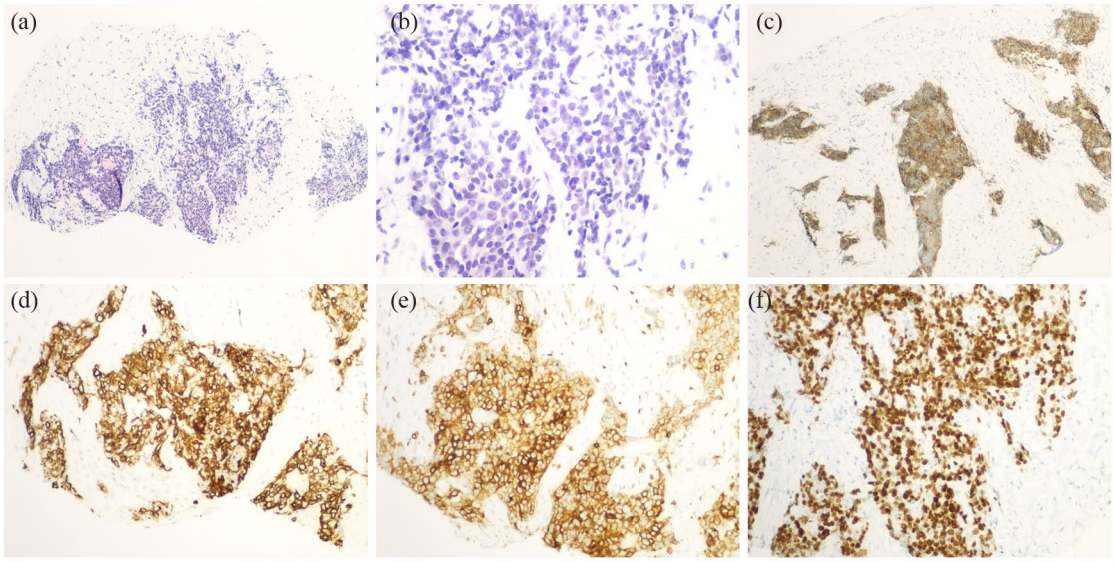

Figure 2. Pathology slides of the anterior mediastinal mass. (a) Low power (100x) Hematoxylin and Eosin (H&E) slide showing a nested poorly differentiated carcinoma with a marked desmoplastic stroma. (b) High power (400x) H&E slide. (c) Immunohistochemistry (IHC) stain of PD-L1 showing 100% expression (100x). (d) IHC stain of cytokeratin AE1.3 confirms carcinoma (200x). (e) IHC stain of CD5 confirms thymic origin (200x). (f) IHC stain of P40 confirms squamous type (200x).

Our patient had a complete response to pembrolizumab therapy, although he experienced significant complications at two notable timepoints (Table 1). Shortly after initiating pembrolizumab, our patient developed symptomatic thyroiditis, atrial fibrillation and transaminitis. After thorough evaluation and consultation among his medical oncologist, cardiologist and endocrinologist, these symptoms were attributed to immune-related adverse events (irAEs) associated with pembrolizumab therapy. Effective management was achieved through a corticosteroid taper and long-term levothyroxine supplementation.

Approximately 2 years after pembrolizumab initiation, our patient reported headaches, fatigue, joint pain and muscle fasciculations. To investigate the underlying cause of these symptoms, a comprehensive neurologic and rheumatologic evaluation was initiated. During this period, the patient experienced severe lightheadedness, and was found to have second-degree heart block. While his neurologic work-up was unrevealing, serologic testing indicated the presence of ANA, anti-RNP, anti-chromatin and anti-Ro autoantibodies, suggesting the presence of a mixed connective tissue disease. Additionally, the work-up incidentally revealed positive Lyme titers. Despite the absence of the characteristic erythema migrans rash, a concomitant diagnosis of Lyme disease was considered given the patient's residence in an endemic area and the presence of second-degree heart block.

Despite completing a course of antibiotics directed towards Lyme disease, the patient continued to have intermittent fasciculations, fevers, headaches and persistently elevated autoantibodies. The persistence of these constitutional symptoms and elevated autoantibodies refractory to antibiotics were concerning for a heightened state of autoimmunity presumably due to immunotherapy. Consequently, the patient, together with his rheumatologist and medical oncologist, made the decision to discontinue pembrolizumab as he had already completed the recommended 24 months duration of immunotherapy for other malignancies and had no evidence of disease on surveillance scans.[8–10] His constitutional symptoms improved with a corticosteroid regimen tapered over a few weeks and he sustained a complete response for a total of 38 months.

Fourteen months after treatment cessation, a surveillance PET-CT showed a hypermetabolic portocaval LN positive for metastatic TC [Figure 1(d)]. Following laparoscopic resection and confirmed 100% PD-L1 expression, the patient was

Table 1. Significant events during pembrolizumab therapy.

Event	Onset of irAEs	Work-up	Evaluations	Interventions	Notes
Thyroiditis	Cycle 2	T4 20.4 µg/dL, T3 252 ng/dL, Thyroid-stimulating hormone (TSH) < 0.01 µIU/mL, thyroglobulin Ab 524 IU/mL, thyroid peroxidase Ab 362 IU/mL. Following steroid taper: TSH 62 µIU/mL	Cardiology/ electrophysiology, endocrinology, medical oncology	Prednisone 20 mg taper over 2 weeks. Levothyroxine 50–120 µg	Initial hyperthyroid state completely resolved with steroid taper after 2 weeks and developed into hypothyroid state requiring long-term levothyroxine supplementation
Atrial fibrillation		electrocardiogram (ECG), electrophysiology work-up			
Transaminitis		63 U/L AST, 189 U/L ALT			
Headaches/ fasciculations	Cycle 24	Negative magnetic resonance imaging (MRI) head/neck, negative electromyography (EMG)	Neurology, cardiology/ electrophysiology, infectious disease, rheumatology, medical oncology	Doxycycline, ceftriaxone. Prednisone 35 mg (0.5 mg/kg) taper over 6 weeks	Persisted after course of antibiotics for Lyme disease
Second-degree heart block		ECG, positive Lyme IgM/IgG			Completely resolved with antibiotics for Lyme disease
Elevated autoantibodies		antinuclear antibody (ANA) 1:640, antinuclear ribonucleoprotein antibody (anti-RNP) > 8.0 AI, anti-chromatin 3.2 AI, anti-Ro 101 AI			No symptoms associated with a specific mixed connective tissue disease

irAEs, immune-related adverse events.

restarted on pembrolizumab based on his prior complete response. He was monitored closely by his rheumatologist in the context of markedly elevated autoantibodies. Since initiation, the patient has experienced symptomatic pericarditis managed with a similar course of corticosteroids. Currently, 5 years after initial diagnosis, the patient has maintained his career as an associate dean of a medical school and remained physically active, with no evidence of disease for 16 months.

Discussion

We present a unique case of recurrent metastatic TC that showed an impressive response to pembrolizumab immunotherapy after achieving a prior complete response. Pembrolizumab is a monoclonal antibody targeting programmed cell death-1 (PD-1), an immune checkpoint receptor expressed on activated *T* cells. Tumor cells with progammed death-ligand 1 (PD-L1) are able to bind to PD-1 receptors on activated *T* ccells and induce programmed cell death. By blocking PD-1 receptors, pembrolizumab enhances the vulnerability of these tumor cells to T-cell-mediated antitumor immunity. TETs commonly express PD-1,[11] making PD-1 immune checkpoint inhibitors such as pembrolizumab a promising option for advanced TC that has been refractory to first-line platinum-based therapy. Phase II trials have demonstrated an overall response rate of 19.2–22.5% in TC patients treated with pembrolizumab, with stronger responses observed in cases with higher PD-L1 immunohistochemical expression.[7,12] Our case aligns with these findings, as our patient's tumor exhibited 100% PD-L1 expression and achieved a complete response after progression following an initial cisplatin-docetaxel regimen. Based on this initial success, the patient and his medical team decided to reinitiate pembrolizumab after his second recurrence despite markedly elevated autoantibodies.

The optimal duration of pembrolizumab therapy for TC has not been established, although a 24 months treatment period is recommended for

other thoracic malignancies such as lung cancer. Phase II trials in TC have reported median treatment durations of 6–8 cycles,[7,12] with discontinuation occurring due to disease progression or severe irAEs. In our case, pembrolizumab was discontinued after 24 months due to concerns of heightened immune reactivity associated with elevated autoantibodies. The intricate relationship among immune checkpoint inhibitors, irAEs and elevated autoantibodies is not fully elucidated. Although the occurrence of irAEs with immune checkpoint inhibitors is well documented, the underlying mechanism remains unclear. Current hypotheses suggest that irAEs arise from disturbances in immune homeostasis and the subsequent loss of self-tolerance. Different types of immunotherapy, such as anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) *versus* anti-PD-1 therapy, are associated with different irAE profiles, indicating that irAEs are caused by the mechanism of immune dysfunction rather than the tumor type.[13,14] Interestingly, thymic epithelial malignancies have a higher incidence of severe irAEs compared to other solid malignancies.[15] This suggests a baseline immune dysregulation in TETs that is further exacerbated by immune checkpoint inhibitors.[6] Prevailing hypotheses include the 'escape' of thymoma-derived lymphocytes before undergoing self-tolerance, genetic changes in TETs that alter T-cell development and induce self-reactivity, or defects in the antigen-presenting autoimmune regulator gene.[6] Notably, among TETs, thymomas have a higher incidence of irAEs than TC.[7] The apparent heightened immune dysregulation in thymomas is consistent with their unique associations with autoimmune PNS and EM.[2,3,16]

Several studies have reported that irAEs may be associated with improved patient outcomes, including progression-free survival, overall response rate and overall survival.[17–19] Importantly, one retrospective study found that this association was not affected by treatment of irAEs with corticosteroids.[18] These findings suggest that irAEs could potentially serve as a biomarker for anti-tumor immunity, and the beneficial effect of immune checkpoint inhibitors is not diminished by the corticosteroids used to manage irAEs.[20] However, further exploration is required to uncover these immunological mechanisms and fully understand these relationships. Of note, our patient was also found to have elevated autoantibodies following initiation of pembrolizumab immunotherapy, which was concerning for the increasing autoimmunity and development of a mixed connective tissue disease though he did not have symptoms indicative of a specific disease. Studies have not established a clear relationship between elevated autoantibodies and incidence of irAEs, and contradictory results exist regarding their impact on patient outcomes.[19,21,22] Notably, our patient initially presented with Raynaud's phenomenon, which is typically associated with mixed connective tissue disease.[23] It is challenging to determine whether our patient's Raynaud's phenomenon was related to the immune dysregulation of TC or represented a predisposition to autoimmunity that was further exacerbated with immune checkpoint inhibitors. It is also possible that the Raynaud's phenomenon was an independent and coincidental condition. Interestingly, our patient did report symptom improvement after the initial chemotherapy regimen and denies any exacerbations when he had Lyme disease. This case emphasizes the importance of pretreatment assessments for autoantibodies to gain further insights into the potential relationship between elevated autoantibodies and worsening immune dysfunction.

Throughout the treatment course, our patient encountered multiple irAEs in addition to diagnoses of Raynaud's phenomenon and sigmoid colon adenocarcinoma. In the face of a rare, aggressive tumor and this unique presentation, a multidisciplinary approach was adopted to promote synergy among his treatment regimens and prioritize the patient's quality of life. The care team involved specialists from various disciplines, including a thoracic medical oncologist, radiation oncologist, thoracic surgeon, cardiologist, neurologist, rheumatologist, endocrinologist and an infectious disease specialist. The multidisciplinary team effectively managed all irAEs with supportive medications, hormone replacements and short courses of corticosteroids to enable the continuation of pembrolizumab treatment for the standard duration of 2 years. The decision to restart immunotherapy upon the patient's second recurrence was carefully deliberated, but ultimately, pembrolizumab was reintroduced with close monitoring by the multidisciplinary team. The comprehensive oversight played a crucial role in navigating the complexities of our patient's condition and ensuring the best possible outcome.

Patient's perspective

The patient is an associate dean as well as an associate professor of science education and

laboratory science at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. He has provided his experiences and perspectives of his disease course to demonstrate the emotional impact of having a rare form of cancer, particularly as a pathologist and medical educator himself, and highlight the support he has received.

For the better part of a year and a half, I had noticed these weird myalgias in my upper body. At the same time, roughly, I developed a very severe case of Raynaud's. I went for a Raynaud's work-up, which was a battery of tests and a chest X-ray. Afterwards, I was brought into the radiology suite. I saw an X-ray on the light board with a huge mediastinal mass, and I said to the radiologist, 'Please tell me that's not mine'. By Saturday, I had the diagnosis of a high grade, poorly differentiated squamous carcinoma of thymic origin, otherwise known as a TC. The days after I got the diagnosis were not good. I started to read a little bit, and I shouldn't have done that. I knew enough about medical oncology to make me dangerous. But I decided very early on that I was not going to be my doctor. I was going to trust my doctors and try hard to not second-guess their judgment.

On Monday, I went to see an oncologist. She looked at me, and I think she saw that I was depressed, but she settled me right down. She said, 'We are not going for just maintaining you for a few years. We are going for a cure'. And the way she said it, I trusted her. She was direct, truthful, knowledgeable. I've noticed that she is kind of like the conductor of this whole thing. I've had multiple different providers because of all the side effects I've experienced. She'll talk to my cardiologist, my surgeon, my rheumatologist and my neurologist. She was on the phone with everybody all the time, so I never felt that I had to re-explain anything to her. I don't think anybody makes a move without at least clearing it with her. In the past, I haven't been the easiest patient at times, asking questions and being overly concerned. But I've been blessed with professionals that are reflective people. If they don't know something, they'll seek it out and search for the answer. If they do know something, they'll act on it. My doctors are not only competent, they have the 'it' factor. They can look in my eyes, and without saying a word, I have full trust and confidence in them. The sheer appreciation I have for the whole team goes without saying.

I think fighting cancer is really two things: It's fighting the side effects of treatment and fighting this whole idea of your own mortality. When I started treatment, I didn't have the energy to do anything. It was an ongoing struggle to even eat. Words mean something in medicine. When somebody says, 'I'm fatigued', what does that actually mean? Before, I could have gone for a five-mile run, and when I came back, I'd be fatigued, but I'd feel great. It's a good fatigue. Or maybe a physician can prescribe me a medication where I might feel fatigued as a side effect. Yeah, I'd feel a little tired but I'd go to sleep and wake up feeling okay. But when I'm on chemo, the fatigue is like this: Even when I go to sleep, I still feel like hell.

It's a little frustrating for me to play Whack-a-mole with the side effects from the Keytruda (pembrolizumab) but I'll be on it indefinitely. I tried coming off of it before but (the cancer) came back. It's one of those things where the treatment regimen seems to work and I'll get steroids or other medicines to alleviate symptoms. It's just part of the deal. I'll take anything as long as I have negative scans.

Honestly, the mental part of the deal is just as tough as any other physical ailment. (The idea of your mortality) is always in the back of your mind. Negative thoughts. I'm human. It's almost like you're on a hike and there's like a little pebble in your shoe, and it's not bothering you enough to take off your shoe in the middle of the street, but you just know it's there. I've pretty much reconciled that there'll be weeks or days that I'll feel great and won't think about it much, or weeks and days that I think about it quite a bit.

After 5 years, I'm still figuring out the best way to deal with all of this. I overcompensate by making sure I'm incredibly busy at work, signing up for everything like I did 10 years ago. When I'm at work, I tend not to think about it as much. Having the opportunity to teach sessions was just as important as the drugs going into me. If I'm working, I'm going to go in with a smile and I'm going to try to demonstrate that everybody's entitled to have bad days or bad years, but that's not an excuse for not fulfilling your responsibilities in my case as a provider and an educator. So in that way I deal with it, and I try to deal with it by

eating properly, going for long walks. . . if I feel like I can get a good tired by walking around or doing things I can control, I do a good job in making sure I do that.

I think what's changed is that I'm a little bit more tired. The mental awareness of having to deal with something chronically chips away at you over time. When you pull a rubber band back a hundred times, the rubber band never gets back to the exact same place. That's kind of where I'm at. But I have a choice to dwell on it or to move on. Whatever is happening, there's enough good going on, and I have a positive attitude. I'm thankful for my family and doctors, I wouldn't be here without them. I'm thankful for the opportunity to continue to teach medical students and have them learn from my experience.

Conclusions

This case describes the use of the anti-PD1 monoclonal antibody pembrolizumab to achieve a disease-free state in an advanced stage IVb TC. Pretreatment assessments and multidisciplinary input to monitor and tackle irAEs are extremely important. This case highlights the utility of an individualized, multidisciplinary approach to treat a rare and aggressive tumor with a complicated disease course. The coordinated efforts of various specialists along with patient's persistence, partnership and solid resolve helped achieve the patient's priority of staying alive 5 years and beyond while maintaining a very high quality of life.

Declarations

Ethics approval and consent to participate

Ethics approval is not applicable due to institutional/IRB policy for single case reports. The patient involved in the case report gave written informed consent to participate in the study.

Consent for publication

The patient involved in the case report gave his written informed consent authorizing use, disclosure, and publication of his health information.

Author contributions

Carol Wang: Conceptualization; Visualization; Writing – original draft; Writing – review & editing.

David Erick Elkowitz: Conceptualization; Supervision; Writing – review & editing.

Michael John Esposito: Data curation; Resources; Writing – review & editing.

Rakesh Dinesh Shah: Data curation; Resources; Writing – review & editing.

Henry Tannous: Data curation; Writing – review & editing.

Maria-Louise Barilla-Labarca: Data curation; Writing – review & editing.

Nagashree Seetharamu: Conceptualization; Supervision; Writing – review & editing.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data and materials used in this case report are based on the medical records, imaging studies and pathological findings of our patient. Due to privacy and confidentiality considerations, access to the specific patient data and materials is restricted. Upon reasonable request, anonymized and de-identified data may be made available for research purposes, in compliance with institutional policies and ethical guidelines.

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