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ABSTRACT

Introduction

In recent years cancer immunotherapy has emerged as a 'game changer' in the arena of cancer therapeutics. Immune checkpoint blockade therapy in particular has been one of the most impressive advancements. By unleashing the host immune system against malignant cells, unprecedented survival rates and durable clinical responses are now being reported. These novel agents however are also associated with a unique spectrum of side effects. Thus increasing use of immunotherapy merits familiarity with the clinical features of these adverse events and their subsequent management.

Case Report

Our case involves a 58 year old gentleman diagnosed with metastatic adenocarcinoma of the lung who received nivolumab as second line treatment with a good partial response. His treatment was complicated by hypothyroidism and pneumonitis, the latter immune-mediated adverse event resulting in discontinuation of treatment. However six months after treatment cessation, the patient continues to respond radiologically and remains clinically well.

Conclusion

This case highlights the efficacy of immunotherapy, but also the difficulty in detecting and managing their unique side effects.

Keywords: Lung cancer; nivolumab; anti-PD1; immunotherapy; pneumonitis

INTRODUCTION

The introduction of immunotherapy as a novel treatment modality for cancer has generated great interest and excitement over the last few years. By harnessing the exquisite specificity, potency, and memory of the hosts' immune system to seek out and destroy cancer cells, immunomodulatory agents have demonstrated efficacy in an increasingly wide range of malignancies and their development continues at a breathtaking pace [1]. The clinical validation of monoclonal antibody blocking of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), has been particularly impressive and these therapies have emerged not only as an adjunct to conventional therapy, but they have begun to outperform them.

Historically for patients with advanced non-squamous non–small-cell lung cancer (NSCLC) progressing after platinum-based chemotherapy treatment, effective second line options were limited. However in 2015 nivolumab, an immune checkpoint PD-1 inhibitor, was approved by the U.S Food and Drug Administration (FDA) for treatment in this cohort [2]. By binding to and blocking the PD-1 receptor, nivolumab prevents any interaction with its ligand PD-L1, thus reversing tumour-induced suppression of tumour specific T cells.

However these novel agents are associated with a unique spectrum of side effects. Almost any organ may be affected and toxicity may be a limiting factor in its use. Immune mediated pneumonitis is rare, and there is little published data with regards to distinguishing features [3]. However if undetected it may result in devastating consequences, thus familiarity with, and early recognition, of these adverse events is critical.

Treatment often involves immediate withdrawal of the offending agent and the initiation of glucocorticoids if clinically warranted. However despite discontinuation of treatment, immunotherapy displays another remarkable feature in its ability to provide a durable clinical and radiological response that may be observed years later [4].

CASE REPORT

A 58 year old gentleman presented with a six month history of progressive, left sided

chest pain, radiating to the left side of his neck. He also complained of a four month history of left neck swelling and associated dysphagia, as well as intermittent hoarseness.

His background was significant for hypertension and non-insulin dependant diabetes mellitus. He was a heavy smoker with a 40 pack year history. He was unemployed but previously worked as a welder.

Physical examination revealed a well appearing gentleman with an excellent performance status. There was an enlarged, palpable, 3 x 3cm left supraclavicular lymph node noted but the remainder of the examination was unremarkable.

A chest radiograph (CXR) revealed a small nodular density in the left upper lobe, and this was further characterised as a 2cm solid lesion suspicious for malignancy on computed tomography (CT) of the thorax [Figure 1]. A smaller satellite nodule was also observed in the same lobe. In addition there was significant mediastinal lymphadenopathy causing left vocal cord palsy. A CT Neck also revealed an enlarged, 24 millimetre (mm) left supraclavicular lymph node [Figure 1]. A CT Brain was normal.

Fine needle aspiration (FNA) of the supraclavicular lymph node revealed a diagnosis of metastatic adenocarcinoma of the lung with signet ring features [Figure 2]. A tru-cut biopsy was requested to facilitate molecular analysis however no EGFR mutation nor ALK gene rearrangement was detected.

The patient was discussed at a multidisciplinary meeting and was deemed surgically inoperable with T3 N3, or Stage IIIb, adenocarcinoma of the lung. Spread to the supraclavicular lymph node also ruled out radical radiotherapy however he was counselled for palliative radiotherapy, and received 30 Gray (Gy) in 10 fractions. This was followed by palliative chemotherapy in the form of cisplatin and pemetrexed, and he received six cycles which were well tolerated. A re-staging CT scan reported a good partial response, with complete resolution of the mediastinal and left supraclavicular lymphadenopathy. The patient declined maintenance pemetrexed.

He remained on surveillance with three-monthly clinic visits however eight months after completion of treatment he reported intermittent episodes of sharp chest pain at rest, increasing non-productive cough and a three kilogram (kg) weight loss over three months. CXR revealed increasing left hilar lymphadenopathy, and a

subsequent CT thorax abdomen and pelvis (TAP) confirmed progressive disease with left bronchopulmonary and left anterior mediastinal lymphadenopathy, as well as aortopulmonary and subcarinal adenopathy. There was also interval development of bulky, bilateral adrenal gland enlargement.

The patient was commenced on nivolumab as part of the expanded access programme and had a good partial response post six cycles, with improvement in the mediastinal adenopathy and in the adrenal lesions. After 13 cycles he began to complain of increasing fatigue. Thyroid function tests were requested and he was diagnosed with hypothyroidism (TSH <0.05 mU/L and T4 18.3 pmol/L). He was commenced on thyroid hormone replacement, 75 mcg levothyroxine, with symptom relief. After 14 cycles he began to complain of increasing dyspnoea. A CT thorax reported new bilateral airspace opacification in a paramediastinal anterior and posterior distribution [Figure 3]. The differential diagnosis included infection and endobronchial spread of the tumour, however given the clinical presentation an immune-mediated drug reaction was felt to be the most likely diagnosis. Nivolumab was subsequently discontinued and he was commenced on a reducing dose of prednisolone (1mg/kg/day) with immediate symptom relief.

He remained under close surveillance and ten weeks later he was offered a re-introduction of nivolumab however he declined and chose to remain on surveillance. Six months later he remains clinically well. Remarkably his most recent CXR shows an ongoing radiological response with reduction in the mediastinal lymphadenopathy despite discontinuing treatment six months previously [Figure 4].

DISCUSSION

The idea of exploiting our immune system to target cancer cells was first proposed by Ehrlich in 1909, and the concept of immune surveillance was further formulated by Burnet in 1957 [5,6]. The theory suggests that nascent transformed cells arise continuously in our bodies due to carcinogens, radiation, inflammation and inherited mutations, and speculates that immune cells act as sentinels, seeking out and destroying these transformed cells before they become clinically evident [1, 5-8]. Cancer immune surveillance is considered to be an important host protection process to inhibit carcinogenesis and to maintain regular cellular homeostasis [8].

Advances in our understanding of tumour immunology has led to the proposal of three essential phases in the interaction between host and tumour cells: elimination, equilibrium and escape.

The innate immune response is the first line of defense against these transformed cells, and elimination is achieved by immune effector cells such as natural killer (NK) cells and by secreted cytokines such as IFN-γ. However *elimination* results in immune selection, decreasing immunogenicity and ultimately resulting in immune resistance [8]. This is known as the *equilibrium* phase. Finally as the tumour progresses, multiple mechanisms of resistance develop, such as immune checkpoint dysregulation, allowing the tumour to *escape* detection and destruction [8,9].

To combat the 'three E's', immunotherapy has emerged as an exciting new treatment approach. The notion of restoring the hosts' natural defence mechanisms and activating the immune system to specifically target these cancer cells has been met with great interest and enthusiasm. The development of immune checkpoint inhibitors in particular has had a profound impact on modern cancer therapeutics. By blocking immune-inhibitory pathways activated by these cancer cells, we can 'release the brakes' and unleash our immune system to target and destroy these malignant cells.

These agents first gained acceptance in the clinical domain after their success in advanced non-BRAF-mutated malignant melanoma, a disease historically associated with a grim prognosis [10]. The introduction of these agents as a novel treatment modality for these patients has resulted in unprecedented survival rates and has revolutionised how we now approach and manage these malignancies. This success has led to the exploration of its use in other cancer types.

Like in advanced melanoma, effective treatment options were limited for patients with non-squamous non–small-cell lung cancer (NSCLC) whose disease progresses after first-line chemotherapy. However in October 2015 the FDA granted approval to nivolumab as a second line agent in metastatic NSCLC based on results from the CHECKMATE 057 trial [2]. This randomised, phase III trial involved 582 patients and compared nivolumab to the standard of care at that time, docetaxel. The study favoured nivolumab in response rate (19% vs 12%) as well as median overall survival (12.2 months vs 9.4 months). Nivolumab was also associated with a more

favourable toxicity profile.

Nivolumab is a fully human, IgG4 PD-1 immune checkpoint inhibitor antibody. PD-1 is a protein expressed on the surface of activated T cells. When bound to its ligand PD-L1, expressed on antigen presenting cells, the T cells become inactive. This is one way in which the body regulates the immune system, and to prevent uncontrolled T cell activation. However many cancer cells also express PDL-1, thus enabling them to evade attack by T cells. Anti-PD-1 antibodies like nivolumab aim to block this PD-1/PDL-1 interaction, resulting in the preferential activation of T cells with specificity for the cancer cells [11,12]. Nivolumab has been shown to be effective in a wide range of malignancies, and has been FDA approved for the treatment of melanoma [10, 13], renal cell cancer [14], Hodgkin lymphoma [15] and squamous cell lung cancer [16].

Immunotherapy however is not without side effects, and any organ may be affected. With increasing use of these agents clinical suspicion and awareness of any adverse events is paramount and warrants a critical need for familiarity with the clinical features of toxicity and their subsequent management.

Endocrinopathies, particularly hypothyroidism, are common. Median time to onset is variable. The majority are grade 1-2 (as per CTCAE v4.0) and symptoms can usually be navigated with hormone replacement therapy. In the present case, our patient experienced hypothyroidism after 13 cycles of nivolumab. In the aforementioned CHECKMATE 057 trial, 7% (20/287 patients) experienced hypothyroidism, with a median time to onset 2.9 months (range 1.4-11.8) [2]. Table 1 displays a selection of immunotherapy trials and the incidence of hypothyroidism [Table 1].

Immune mediated pneumonitis however is rare, and has only been described in isolated case reports and small case series [3, 12, 19-21]. A large meta analysis by Peng et al. (2016) included 5005 patients from 15 clinical trials and reported an incidence of 2.9% and 1.8% for all grade and high grade pneumonitis respectively, while Naidoo et al. report an incidence range between 0-10% [22,23]. The incidence and grade of pneumonitis across selected clinical trials is displayed in table 2 [Table 2].

In another large series by Naidoo et al., 915 patients who received anti–PD-1/PD-L1

monoclonal antibodies were included and pneumonitis was reported in 43 (5%) [3]. Of note incidence appeared to be similar in patients with melanoma and non-small cell lung cancer. A higher incidence however was reported in those patients receiving combination immunotherapy (19/199 (10%)) versus monotherapy alone (24 of 716 (3%)). Time to onset was variable, ranging from 9 days to 19.2 months. The majority of cases were grade 1 to 2 (72%), and 86% (37 of 43) improved with discontinuation of treatment and in some cases immunosuppression.

Early diagnosis can be challenging however if undetected it may have devastating consequences, and fatalities have been reported [3,13,17,19]. Diagnosis is usually one of exclusion, and is largely based on clinical and radiological findings. In the present case, while bronchoscopy to exclude infection was not performed, our patients' symptoms and imaging were compatible with immune-mediated pneumonitis, while the rapid resolution of symptoms after glucocorticoid therapy adding further support to our diagnosis.

In general, protocols for the management of immune-related adverse events require withdrawal of the offending agent and the use of corticosteroid immunosuppression (prednisone 0.5 mg/kg/day) in moderate to severe cases. Treatment re-introduction can be considered upon resolution of symptoms. In cases of severe or life threatening immune-mediated toxicity (grade 3 or 4) permanent discontinuation is advised and higher doses of corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) may be required. If symptoms persist, additional immunosuppressants such as infliximab, cyclophosphamide or mycophenylate mofetil may be warranted.

There is increasing data however to suggest that even after discontinuation of treatment, patients may derive a durable clinical benefit seen for many years [4]. In the aforementioned CHECKMATE 057 trial, the median number of doses given was six and remarkably the median duration of response was 17.2 months (range, 1.8-22.6 months) [2]. The clinical activity across selected trials is shown below [Table3]. In the present study our patient discontinued treatment after 14 cycles, and continues to respond both clinically and radiologically over six months later.

CONCLUSION

While cancer immunotherapy represents an exciting new treatment approach,

unfortunately not all patients will respond to these novel treatments. Continued efforts are required, particularly in the identification and validation of predictive biomarkers, thus optimising patient selection and avoiding treatment-related toxicity in patients that are unlikely to benefit.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

AUTHOR'S CONTRIBUTIONS

NOT GIVEN

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TABLES

Table 1: Incidence of immune-mediated hypothyroidism in selected clinical trials

	Clinical Trial	Line of Therapy	All Grades n/N (%)	Grade 2 n/N	Grade 3-5 n/N	Median time to onset, months (range)
Nivolumab	CHECKMATE 057 [2]	2L	20/287 (7%)	-	-	2.9 (1.4-11.8)
Nivolumab	CHECKMATE 017 (SqNSCLC) [16]	2L	5/131 (4%)	-	0/131 (0%)	-
Ipilimumab and Nivolumab	CHECKMATE 069+067 (Melanoma) [13,17]	1L	89/407 (22%)	47/407 (12%)	Grade 3: 6/407	2.1 (1 day -10.1 months)
Nivolumab	CHECKMATE 025 (Renal) [14]	2L	33/406 (8%)	17/406 (4%)	Grade 3: 2/406	4.6 (15 days – 13.6 months)
Pembrolizumab	Keynote 010 [18]	2L	2mg/kg: 28/339 (8%) 10mg/kg: 28/343 (8%)	-	0/339 (0%) 0/343 (0%)	-

Table 2: Incidence of immune-mediated pneumonitis in selected clinical trials

	Clinical Trial	Line of Therapy	All Grades n/N (%)	Grade 2 n/N	Grade 3-5 n/N	Median time to onset, months (range)
Nivolumab	CHECKMATE 057 [2]	2L	10/287 (3.4%)	2/287	Grade 3: 5/287 (2%)	7.2 (2.7-13.1)
Nivolumab	CHECKMATE 017 (SqNSCLC) [16]	2L	6/131 (5%)	1/131	-	0.3-17.6 weeks
Ipilimumab and Nivolumab	CHECKMATE 069+067 (Melanoma) [13,17]	1L	25/407 (6%)	17/407 (4%)	Grade 3: 6/407 (1%) Grade 5: 1/407	1.6 (24 days -10.1 months)
Nivolumab	CHECKMATE 025 (Renal) [14]	2L+	18/406 (4.4%)	12/406 (3%)	Grade 3: 4/406 (1%) Grade 4: 1/406	3.82 (2days-22.3 months)
Pembrolizumab	Keynote 010 [18]	2L	2mg/kg: 16/339 (5%) 10mg/kg: 15/343 (4%)	-	7/339 (2%) 7/343 (2%)	-

Table 3: Clinical activity of immunotherapy agents in selected clinical trials

	Clinical Trial	Line of Therapy	Median Number of doses	Patients with Response	Median time to response	Median duration of response
Nivolumab	CHECKMATE 057 [2]	2L	6 (range, 1-52)	56/292 (19%)	2.1 months (range, 1.2-8.6 months)	17.2 months (range, 1.8-22.6 months)
Nivolumab	CHECKMATE 017 (SqNSCLC) [16]	2L	8	27/135 (20%)	2.2 months (range, 1.6-11.8 months)	Not Reached (range, 2.9-20.5+) + indicates ongoing response
Ipilimumab and Nivolumab	CHECKMATE 069+067 (Melanoma) [13,17]	1L	4 (1-31) 15 (range, 1-38)	44/72 (61%) 138/316 (43.7%)	2.78 months (range, 2.3-12.5)	Not Reached
Nivolumab	CHECKMATE 025 (Renal) [14]	2L+	Median duration 5.5 months	103/410 (25%)	3.5 months (range, 1.4-24.8)	12 months (range, 0-27.6)
Pembrolizumab	Keynote 010 [18]	2L	Median duration 3.5 months	2mg: 42/139 (30%) 10mg: 44/151 (29%)	9 weeks	Not Reached

FIGURE LEGENDS

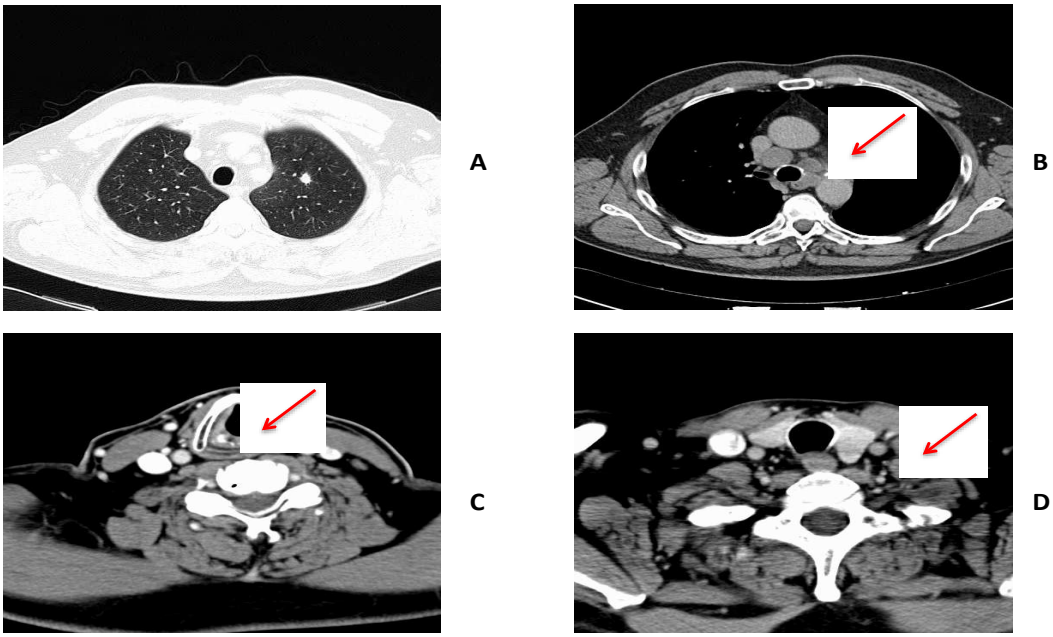
Figure 1 (A-D): CT Neck and Thorax revealed a 2cm solid lesion in the left upper lobe (A) with significant mediastinal lymphadenopathy (red arrow) (B) causing left vocal cord paralysis (red arrow) (C). There was also a 24mm left sided supraclavicular lymphadenopathy (red arrow) (D)

Figure 2 (A, B): Fine needle aspiration (FNA) of the left supraclavicular lymph node revealed a diagnosis of metastatic adenocarcinoma of the lung with signet ring features. (A) H&E stain. (B) TTF1 positive

Figure 3 (A, B): A re-staging CT thorax revealed new bilateral airspace opacification in a paramediastinal anterior and posterior distribution. The differential diagnosis includes infection, endobronchial spread of the tumour and an immune mediated drug reaction

Figure 4 (A-C): Chest radiograph prior to commencing nivolumab showing increasing left hilar lymphadenopathy (A). B) Decreasing size of left hilar lymphadenopathy three months after discontinuation of nivolumab. C) Continued radiological improvement in central mediastinal and left hilar mass six months after discontinuation of nivolumab

FIGURES



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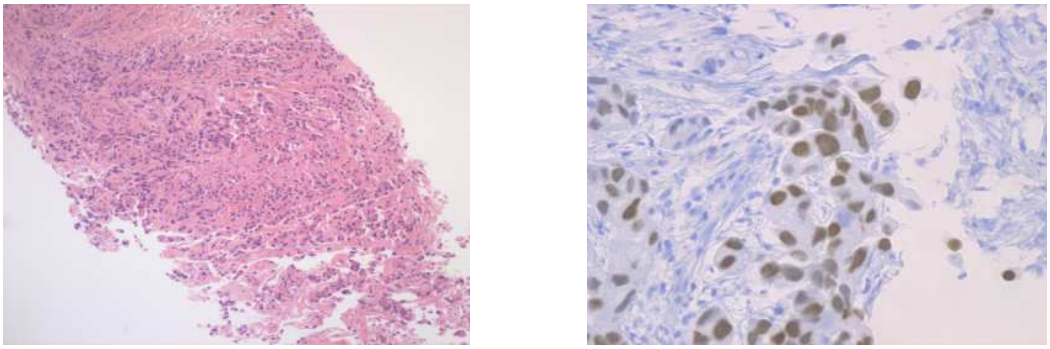

A B

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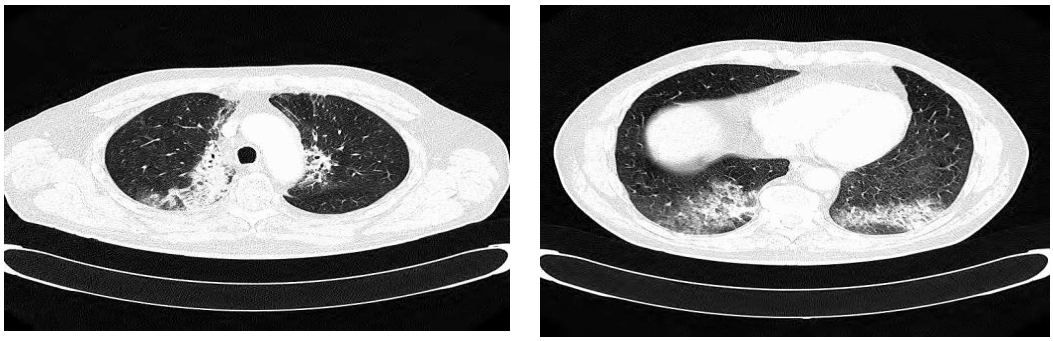
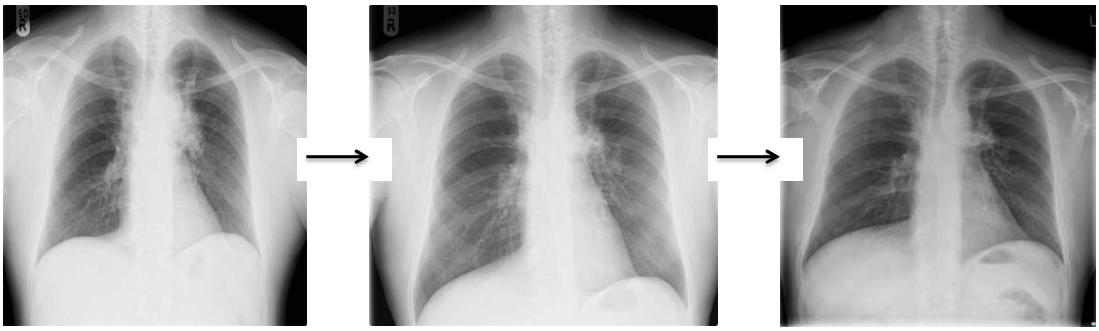


A B

Figure 3 (A, B): A re-staging CT thorax revealed new bilateral airspace opacification in a paramediastinal anterior and posterior distribution. The differential diagnosis includes infection, endobronchial spread of the tumour and an immune mediated drug reaction



A B C

Figure 4 (A-C): Chest radiograph prior to commencing nivolumab showing increasing left hilar lymphadenopathy (A). B) Decreasing size of left hilar lymphadenopathy three months after discontinuation of nivolumab. C) Continued radiological improvement in central mediastinal and left hilar mass six months after discontinuation of nivolumab