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A rare case of chemotherapy induced phrenic neuropathy

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A B S T R A C T

Background: While chemotherapeutic agents result in an improvement in both disease-free and overall survival in cancer patients, treatment can result in short and long-term complications. One well-known complication is neuropathy which can result from a number of chemotherapeutic agents. However, chemotherapy-induced phrenic neuropathy is an exceedingly rare phenomenon with few cases reported in the literature.
Case: A 34-year-old male with metastatic testicular cancer presented with progressive dyspnea on exertion after initiation of chemotherapy with bleomycin, cisplatin, and etoposide. Multiple diagnostic studies were performed including pulmonary function testing, chest computed tomography, fluoroscopic sniff evaluation, in addition to phrenic nerve electromyography. Based on results of these tests, the diagnosis of chemotherapy-induced phrenic neuropathy was made.
Conclusion: Chemotherapy-induced phrenic neuropathy, although rare, should be considered as a cause of dyspnea in cancer patients following initiation of chemotherapy.

1. Introduction

Chemotherapy-induced peripheral neuropathy is a well described sequela of several chemotherapeutic agents that can significantly impact the quality of life in affected patients. It can lead to permanent symptoms and disability in up to 40% of cancer survivors [1]. It is a known complication in many chemotherapeutic agents particularly with platinum based agents, taxanes, vinca alkaloids, thalidomide, and bortezomib [1]. Chemotherapeutic agents typically result in sensory neuropathy while motor neuropathy is less common. Moreover, chemotherapy-induced phrenic nerve neuropathy is very rare. We hereby report a case of chemotherapy-induced phrenic nerve neuropathy in a male patient who presented with dyspnea after being treated with bleomycin, cisplatin, and etoposide for metastatic testicular cancer.

2. Case

A 34-year-old male with a metastatic right testicular cancer presented with a three-month history of progressive dyspnea on exertion. He had undergone right orchiectomy and had received four cycles of chemotherapy with bleomycin, cisplatin, and etoposide. Symptoms were first noted during the final cycle of chemotherapy, and continued to progress over two months. Physical examination was notable for clear lungs on auscultation with no evidence of diaphragmatic paradox.

Pulmonary function testing showed a restrictive pattern, with low maximal inspiratory and expiratory pressures (Fig. 1). Chest computed tomography (CT) scan showed bibasilar atelectasis with low lung volumes on scout film when compared to a prior chest x-ray (Fig. 2). Fluoroscopic sniff evaluation demonstrated evidence of right greater than left diaphragmatic weakness. Phrenic nerve electromyography (EMG), while within normal limits, was notable for asymmetric right side predominant nerve conduction discrepancies consistent with possible fascicular phrenic neuropathy. The constellation of temporal onset of clinical symptoms after chemotherapy along with the fluoroscopy and EMG findings were consistent with diaphragmatic weakness secondary to drug-induced phrenic neuropathy.

3. Discussion

Phrenic nerve neuropathy and diaphragmatic dysfunction can occur from a variety of causes. It most commonly occurs due to direct neoplastic invasion of the phrenic nerve or due to iatrogenic injury during surgery [2]. It can also occur due to infectious neuritis (such as in herpes zoster infections), trauma, in addition to neurologic disorders (such as Guillain-Barré Syndrome), amongst others [2]. Patients with unilateral phrenic nerve paralysis are typically asymptomatic but may

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	PREDICTED	CONTROL
Patient Position		Sitting

LUNG VOLUMES (Pleth)

	NORMAL	LLN	FOUND	%PRED
TLC	8.96	7.80	5.24	58 %
VC	7.19	5.77	3.52	49 %
FRCpleth	3.91	2.93	3.16	81 %

	NORMAL	ULN	FOUND	%PRED.
RV	2.15	2.82	1.72	80 %
RV % TLC	27	36	33	121 %

SPIROMETRY

	NORMAL	LLN	FOUND	%PRED.
VC MAX	7.19	5.77	3.24	45 %
FVC	7.19	5.77	3.22	45 %
FEV 1	5.74	4.56	2.60	45 %
FEV1/FVC	80.4	69.9	80.8	101 %
FEF25-75%	5.37	3.26	2.53	47 %
PEF	11.7	8.3	6.9	59 %
FET			6.49	
MVV	202	169	109	54 %

DIFFUSION CAPACITY

	NORMAL	LLN	FOUND	%PRED.
DLCO_SB	38.1	30.1	18.1	47 %
DLCOcSB	38.1	30.1	20.3	53 %
Hb			11.30	
VA_SB	8.27	7.19	4.64	56 %

Fig. 1. Pulmonary function test showing a restrictive pattern, with low maximal inspiratory and expiratory pressures.

present with dyspnea which can worsen in the supine position [2,3]. Those with bilateral phrenic nerve paralysis are typically much more symptomatic and are at risk for developing sleep-disordered breathing [4]. On examination, decreased diaphragmatic excursion may be seen and the presence of abdominal paradox is considered a classic sign of diaphragmatic dysfunction [2].

When suspected, a number of tests can help establish the diagnosis. Plain chest radiography can show elevation of the diaphragm, fluoroscopy can be used to demonstrate paradoxical diaphragmatic motion using the sniff test, and pulmonary function testing typically shows a restrictive pattern with further reduction in the vital capacity in the

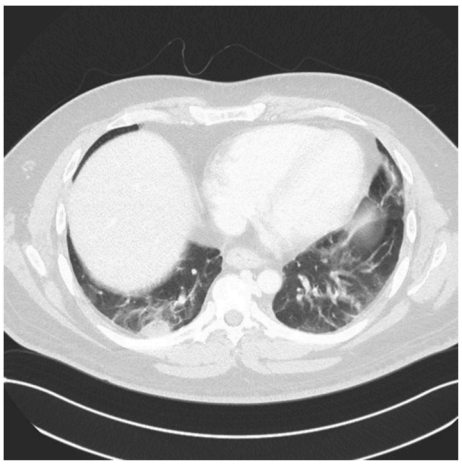

Fig. 2b. Chest CT showing bibasilar atelectasis.

supine position [2,5]. Ultrasonography of the diaphragm can be used to measure the diaphragmatic thickness during breathing with lack of diaphragmatic thickening being an indication of diaphragmatic paralysis [6]. Phrenic nerve EMG is an invasive method to establish the diagnosis, however; this can be technically challenging and is not readily available at all institutions [2]. Finally, measurement of the trans-diaphragmatic pressure is another invasive test that is considered the gold standard for diagnosis but it is not widely used as it can be challenging to perform and interpret [2,7].

While sensory neurotoxicity is a common occurrence following exposure to platinum-based agents, motor neuropathy is uncommon. Furthermore, chemotherapy-induced phrenic nerve motor neuropathy is an exceedingly rare phenomenon, with very few cases reported in the literature [8–11]. Of those cases only one case described phrenic neuropathy associated with a regimen that included a platinum-based agent [12]. The exact mechanism of neuropathy induced by platinum-based chemotherapeutics is not yet fully understood. Chemotherapy-induced alternations of mitochondria, membrane ion channels, intracellular signaling, and neurotransmission can ultimately lead to axonal degeneration, DNA damage, and neuroinflammation with resultant neuropathy [13].

4. Conclusion

In summary, we present a case of chemotherapy induced phrenic neuropathy leading to diaphragmatic dysfunction and new onset exertional dyspnea. Phrenic nerve neuropathy should be considered as a rare

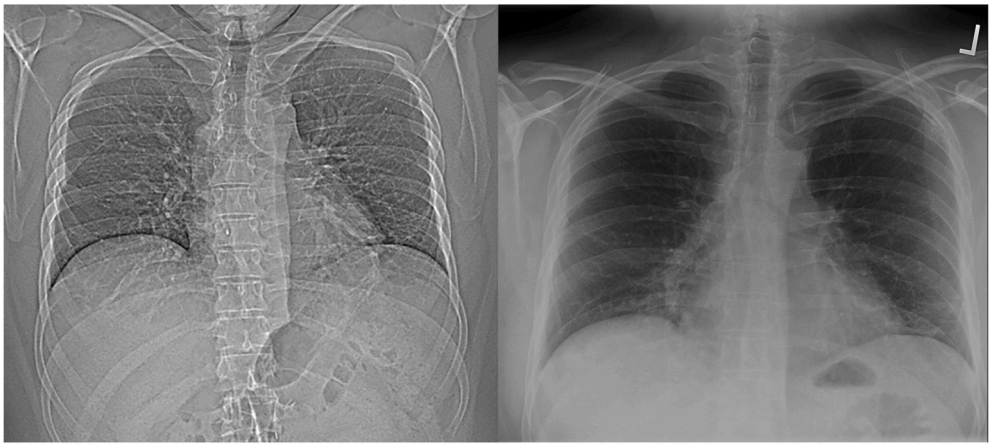

Fig. 2a. Scout film of chest CT after chemotherapy demonstrating low lung volumes compared to prior chest x-ray.

cause of dyspnea in cancer patients following initiation of chemotherapy.

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Author contribution

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Declaration of competing interest

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CRediT authorship contribution statement

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