Acute motor neuropathy with quadriparesis following treatment with triple tyrosine kinase inhibitor, nintedanib

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a rare progressive interstitial lung disease characterized by declining lung function, worsening dyspnea, exercise capacity and poor prognosis with median survival of 3–5 years [1,2]. IPF predominantly affects people over the age of 60, however it has worse prognosis in younger patients with genetic predisposition like short telomere syndrome [3]. Nintedanib, one of two anti-fibrotic therapies approved for IPF treatment, is associated with predominantly gastrointestinal adverse effects with rare neurological side effects like fatigue, dizziness and headaches. Significant polyneuropathy or motor dysfunction is rarely seen. We present the case of a patient who developed quadriparesis following initiation of Nintedanib.

1. Introduction

IPF is a rare progressive interstitial lung disease characterized by declining lung function, worsening dyspnea, exercise capacity and poor prognosis with median survival of 3–5 years [1,2]. IPF predominantly affects people over the age of 60, however it has worse prognosis in younger patients with genetic predisposition like short telomere syndrome [3]. Nintedanib, one of two anti-fibrotic therapies approved for IPF treatment, is associated with predominantly gastrointestinal adverse effects with rare neurological side effects like fatigue, dizziness and headaches [4]. Significant polyneuropathy or motor dysfunction is rarely seen. We present the case of a patient who developed quadriparesis following initiation of Nintedanib.

1.1. Case report

A 39-year-old Caucasian male with suspected familial IPF secondary to short telomere syndrome (telomere length < 1st percentile using flow cytometry and FISH; mom had IPF), was started on Nintedanib for symptomatic progressive fibrosis six months after his initial diagnosis (See Fig. 1–3 for chest computed tomography and telomere length test images, and Table 1 for details of initial work up).

Figures: 1 and 2 showing Bilateral Subpleural honeycombing in axial and coronal views.

24 hours after his first dose of Nintedanib, he developed tingling “pins and needle” sensation in his fingers and toes. This progressed rapidly over the next 2 days to bilateral upper and lower extremity numbness and motor weakness by the 4th day prompting him to seek medical attention. Upon presentation to the emergency department (ED), he was unable to lift his arms against gravity and had had a fall at home due to severe lower extremity motor weakness and loss of sensation in his feet. He took a total of 6 doses of Nintedanib dosed at 150mg twice a day. Prior to initiating Nintedanib, he had no motor or sensory complaints. He had chronic shortness of breath and dry cough from his underlying disease, but otherwise denied any fevers, chills or upper respiratory symptoms. He had multiple loose stools on the first day of symptoms which self-resolved. There was no associated abdominal pain, nausea or vomiting. There was no worsening of his respiratory symptoms. His only other medications were omeprazole for acid reflux and fluticasone for chronic sinusitis. Neurological examination in the ED was notable for areflexia with flaccid paresis in all extremities (Table 2 - shows detailed physical exam).

He had extensive autoimmune and neurological workup which was mostly negative with the exception of marginally decreased IgG subclass 3 and low thiamine levels. Cerebro-spinal fluid analysis from lumbar puncture was unrevealing with normal protein level and white blood cell count. Brain and pan spinal magnetic resonance imaging (MRI) were also unremarkable without any evidence of nerve root enhancement (see Table 3 for details of work up).

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Electrodiagnostic study done 8 days after initial onset of symptoms showed evidence of motor polyneuropathy involving the upper and lower extremities with limited demyelinating features (Table 4A, C, D). It also showed normal upper and lower extremity sensory potentials (Table 4B). Repetitive nerve stimulation did not identify a neuromuscular junction disorder. There was concern that this acute motor neuropathy had possibly been triggered by his new anti-fibrotic therapy.

Intravenous immunoglobulin and plasmapheresis were discussed but not initiated because he began to improve clinically with physical

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**Fig. 1.** Bilateral Subpleural honeycombing in axial view. Figure Legend: High Resolution Chest CT Scan images at diagnosis showing basal predominant honeycomb cystic changes.

**Fig. 2.** Bilateral Subpleural honeycombing in coronal view. Figure Legend: Coronal sections from high resolution Chest CT scan showing basal predominant honeycomb cystic changes. Note relative apical sparing in Figure 2B.

**Fig. 3.** Telomere Length as measured on peripheral blood cells using flow cytometry and fluorescent in situ hybridization (FISH)\(^1\) 1Baerlocher, G., Vulto, I., de Jong, G. et al. Flow cytometry and FISH to measure the average length of telomeres (flow FISH). Nat Protoc 1, 2365-2376 (2006)
Table 1
Initial Work up done at the time of IPF diagnosis.

| Positive Workup: |
|------------------|
| - Aldolase -9.7 (Upper limit of Normal, 8.1) |
| - ESR: 23 (Elevated) |
| - C-Reactive Protein: 6.6 (Elevated) |
| - Immunoglobulin G (IgG) subclass 3: 20, low (22-178) |
| FSH peripheral blood mononuclear cell (PBMC) telomere length study: Abnormally short telomere length (see Fig. 3). |
| Negative workup (Including Autoimmune work up): |
| - Antinuclear Antibody |
| - Anti Double stranded Antibody |
| - Anti Smith Antibody |
| - Anti Scleroderma Antibody |
| - Anti JO-1 Antibody |
| - CO-GM-1 Triad Antibody |
| - Ganglioside GQ1B Antibody |
| - Glomerular membrane Antibody |
| - Immunoglobulin A and G |
| - Paraneoplastic Autoantibody Panel |
| - Rheumatoid Factor |
| - Anti Citrullinated Peptide |
| - U1 RNP Antibody |
| - Anti Sjogren Antibodies (SSA/SSB) |
| - Anti Centromere Antibody |
| - Anti topoisomerase Antibody |
| - HIV |
| - Extended Myositis Panel: SSA-52 IgG Ab, SSA-60 IgG Ab, Smith/RNA OgG Ab, Jo-1 IgG Ab, PL-12 Ab, PL-17 Ab, PL-7 Ab, EI Ab, Oj Ab, SRP Ab, Ku Ab, PM/Sc 100 Ab, Fibrillarin IgG Ab, P155/140 Ab, Mi-2 Ab, TIF-1 gamma Ab, SAE1 Ab, MDA 5 Ab, NXP2 Ab |

Pulmonary Function Test

Forced Vital Capacity (FVC) 2.94L (55% of predicted)
Forced Expiratory Volume in the first second (FEV1) = 2.41L (56% of predicted)
FEV1/FVC = 82

Total Lung Capacity (TLC) = 4.60L (66%)
Diffusion Capacity (DLCO) = 13.63 ml/min/mmHg (42% predicted)
Six-Minute Walk Distance (6MWD) = 506 yard (38% of predicted)
Walked 67% of expected distance with significant desaturation requiring 2L of oxygen via nasal cannula to complete 6MWT.

Table 2
Detailed Physical examination upon presentation.

Admission Vitals: BP 134/99 | Pulse 96 bpm | Temp 36.7 °C (98.8 °F) | Resp 19 bpm | Ht 1.778 m | Wt. 104.5 kg | SpO2 97% | BMI 33.06 kg/m²

General: Well-built obese Caucasian man in no respiratory distress
Eyes: Pupils equal and reactive to light, no conjunctival pallor or scleral icterus
ENT: opharynx without any lesions
Neck: supple, jugular veins not distended
Respiratory: No respiratory distress, bilateral fine velcro crackles in the mid and lower lung zones
CVS: Normal 1st and 2nd heart sounds, no murmurs, rales or gallop, no pedal edema, distal pulses palpable and equal bilaterally
GI: Abdomen non distended, soft, mild epigastric tenderness, nonmoveable bowel sounds
Skin: warm and well perfused, no rashes
Neurology: Alert and oriented to person, place and time. Cranial Nerves: II - Visual fields full to finger confrontation at bedside. Pupils equal and reactive. Discs sharp. CN III, IV and VI - Extraocular movements intact. No nystagmus. V - Sensory branches intact. VII - Face symmetric. VIII - Hearing intact bilaterally. CV IX, X and XII - Tongue, uvula and palate mid position.
Motor Examination: Decreased tone, normal muscle bulk. Power 3/5 in both proximal and distal muscle groups of lower extremities and 4/5 in all upper extremity muscle groups
Coordination: Dymetria on finger-to-nose test bilaterally
Reflexes: Areflexic. Lower extremity fasciculations present.
Sensation: Intact to light touch and temperature but impaired to pin prick in bilateral lower extremities without spinal sensory level
Gait: Wobbly, unsteady gait, barely able to take a few steps without falling

Ht = Height; Wt. = Weight; SPO2 = Oxygen saturation as measured on finger pulse oximetry
bpm = beats per minute; bpm’ = breaths per minute

Table 3
Work up done on admission.

| Normal Work-up |
|----------------|
| - Creatine phosphokinase (CPK) Normal |
| - Erythrocyte sedimentation rate (ESR) normal |
| - Antinuclear Antibody: <40 |
| - Anti-scleroderma Antibody |
| - Anti-native DNA (Double stranded) antibody |
| - Glomerular Basement Antibody |
| - Anti-smooth muscle Antibody |
| - U1 RNP/SNRNP IgG antibody |

Paraneoplastic Antibody Work-up

- Paraneoplastic Antibodies
- CD-GM-Triad Antibody
- Ganglioside GQ1B Antibody

Infectious Work-up:

- Lyme disease IgG and IgM antibodies
- Negative HIV

Nutritional Work-up:

- Normal Vitamin B12 levels

Heavy Metal Screen:

- Negative heavy metal screen

Cerebrospinal Fluid (CSF) Analysis

- CSF Glucose 54- Normal
- CSF Protein 30.5- Normal

Others:

- Complete Blood Count
- Comprehensive chemistry and liver panels
- Hypersensitivity panel
- Serum and Urine Protein electrophoresis
- Elevated C-reactive protein 7.1 (<5 mg/l)
- Low Vitamin B1 (Thiamine) levels <6 (8-30nmol/l)
- Low Immunoglobulin G (IgG) subclass 3: 20 (22-178)
- Abnormal Nerve Conduction Studies (See Table 4A for details)

Other TKIs have also been reported to cause neurotoxicity. Tandetanib, an experimental first generation FLT3 inhibitor, has been shown in experimental studies to cause reversible muscle weakness and electrophysiologic changes consistent with neuromuscular junction dysfunction and peripheral neuropathy.[10] [11,12]. Sunitinib, a therapy and discontinuation of nintedanib. At the time of discharge, he was ambulating with minimal assistance and gradually regained his strength back to baseline over the next 2–3 weeks post discharge.

2. Discussion

Nintedanib is a tyrosine kinase inhibitor (TKI) which works by blocking the receptors of vascular endothelial growth factor (VEGF), fibroblast growth factor, platelet-derived growth factor and β kinase activity. These have been implicated in the pathogenesis of IPF. Nintedanib binds competitively to the adenosine triphosphate binding pocket of these receptors and blocks the intracellular signaling, which is crucial for proliferation, migration, and fibroblast to myofibroblast transformation of lung fibroblasts, thereby inhibiting essential pathways in the pathogenesis of IPF [5].

Nintedanib has been shown to slow the rate of decline in forced vital capacity in IPF [4]. More recently, it has been shown to be efficacious in slowing disease progression in progressive fibrosing I LD of other etiologies [6-8]. With its widening use, it is important to monitor for potential adverse effects aside from what was noted in initial experimental trials of which diarrhea was the commonest [4]. During the experimental phases of the then test drug BIBF 1120 (Nintedanib), rodents and non-rodents who received this medication displayed some elements of neurological toxicity like abnormal gait and paralysis after receiving nintedanib, but these symptoms did not persist [9].

The clinician should be familiar with the side effects of anti-fibrotic agents and be prepared to address the spectrum of potential problems.

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Multitargeted tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumor (GIST) [13], has also been described as a cause of Guillain-Barre syndrome [14].

The mechanism by which Nintedanib may have caused quadriparesis remains unclear but similar to sunitinib, it may be via inhibitory extracellular action against VEGF receptors, thus increasing levels, which is commonly associated with development of different neuropathies [14].

Diagnosis of acute inflammatory demyelinating polyneuropathy (AIDP) is based on clinical presentation and a constellation of findings on electrodiagnostic study including slowed motor conduction velocities, delay latencies, dispersion of responses, conduction block, low distal compound muscle action potential amplitudes, and prolongation of minimum F wave latency. Even though our patient’s electrodiagnostic study had some limited demyelination features like slowed motor conduction velocity and slowed left ulnar motor conduction velocity, left ulnar amplitude is significantly reduced at the elbow by 80% (>20% drop is abnormal) compared to wrist with significant amplitude increase of over 50% and nearly 20m/s conduction velocity increase with stimulation below the elbow consistent with conduction block at the level of the elbow. This could be consistent with demyelination.

| Nerve/Sites | Muscle | Latency Ms | Amplitude MV | Segments | Distance cm | Lat Diff ms | Velocity m/s | Temp °C |
|-------------|--------|------------|--------------|----------|-------------|------------|-------------|--------|
| L. Median- APB | Wrist  | 3.8 | 1.5 | Wrist- APB | 5 | | | 20 |
| R. Median- APB | Wrist  | 3.5 | 2.9 | Wrist-APB | 5 | | | 31.9 |
| L. Ulnar-ADM | Wrist  | 2.8 | 3.6 | Wrist-ADM | 5 | | | 32 |

Table 4A:
Electrodiagnostic motor nerve studies.

| Nerve/Sites | Rec. Site | Peak Lat ms | Amp μV | Segments | Distance cm | Peak Diff ms | Velocity m/s | Temp °C |
|-------------|-----------|-------------|--------|----------|-------------|------------|-------------|--------|
| L. Median-Digit II (Antidromic) | Wrist  | 2.9 | 28 | Wrist- Digit II | 13 | 61 | 31.9 |
| L. Radial- Anatomical Snuff box (Forearm) | Wrist  | 2.2 | 44 | Forearm- Wrist | 10 | 58 | 31.8 |
| L. Median, Ulnar- Transcarpal comparison | Wrist  | 1.7 | 59 | Median Palm- Wrist | 8 | 64 | 32 |
| L. Sural- Ankle (A 7cm, B 14cm, C 21cm) | Calf (A) | 2.2 | 18 | Calf (A)- Lat mall | 7 | 45 | 32 |

Motor nerve studies showing reduced bilateral upper extremity motor amplitudes with borderline left median conduction velocity and slowed left ulnar motor conduction velocity. Left ulnar amplitude is significantly reduced at the elbow by 80% (>20% drop is abnormal) compared to wrist with significant amplitude increase of over 50% and nearly 20m/s conduction velocity increase with stimulation below the elbow consistent with conduction block at the level of the elbow. This could be consistent with demyelination.

Table 4C:
F wave.

| Nerve | F Lateral ms | M Lat Ms | F-M Lat ms |
|-------|--------------|----------|------------|
| L. Tibial- AH | 57.3 | 4.4 | 52.9 |
| L. Ulnar- ADM | 0.0 | 2.9 | 2.9 |

F-wave table showing absence of left ulnar F wave response (which could be consistent with demyelinating or axonal degenerative process. Normal left tibial F-wave latency.

Table 4D:
H reflex.

| Nerve | H Lat ms |  |
|-------|----------|-------|
| Left | Right |
| Tibial- Soleus | 0.0 | 0.0 |

Absent bilateral tibial H reflexes, a demyelinating feature.
knowledge, this is the second reported case of quadriparesis following the use of Nintedanib. Patejdl et al. [15] reported a similar case of quadriparesis that occurred 12 weeks after initiation of Nintedanib. Their patient required plasmapheresis with slow improvement in motor weakness over several months as opposed to our patient whose symptoms started within 24 hours of initiation of therapy and resolved over 3 weeks with withdrawal of medication and supportive management. Our case suggests that neurologic complications associated with Nintedanib could potentially be immediate and have different clinical courses in different patients.

Declarations of interest

None.

Declaration of competing interest

Authors have no conflicts of interest to declare.

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