Paraneoplastic myopathy in pancreatic cancer: a case report and literature review

Jessica Joanne Padniewski, Elizabeth Nelson, Istiaq Mian, Andrew Laczniak, Samuel Ives and Rawad Nasr

ABSTRACT
Dermatomyositis (DM) and polymyositis (PM) are both immune-mediated inflammatory myopathies known to occur in paraneoplastic syndromes associated with a new diagnosis of malignancy, most commonly breast, ovarian, lung, pancreatic, stomach, colorectal, and Non-Hodgkin’s lymphoma in DM and breast, lung, bladder cancer, and Non-Hodgkin’s lymphoma in PM. While inflammatory markers such as creatine kinase (CK) may be elevated with either DM or PM, marked elevation is rare. Herein, we report a case of newly diagnosed pancreatic cancer presenting with inflammatory myopathy and marked CK elevation. We review the frequency of PM as a paraneoplastic syndrome, the association with marked CK elevation, and the association with pancreatic cancer.

1. Case report

A 66-year-old man with a history of diabetes mellitus type 2, hypertension, and hyperlipidemia, presented with severe, bilateral thigh pain. On further history, he reported 6 weeks of generalized fatigue, 4 weeks of progressively worsening weakness and loose stools in the setting of an 18-kg weight loss over the preceding 3 months. The patient had delayed seeking medical attention due to fear of contracting COVID-19 but ultimately presented after an acute worsening of his weakness, resulting in an inability to walk up the stairs in his home. His prior to admission medications included lisinopril, metformin, and atorvastatin, which he had been taking for several years. The patient was a retired teacher and lived with a roommate. He consumed 3–10 alcoholic beverages a week and had quit tobacco smoking 20 years prior. Previously, he had smoked one-half pack per day. His family history was notable for rheumatoid arthritis in his father.

On exam, the patient’s vital signs were normal and physical exams revealed a jaundiced appearance and three-fifths strength to hip flexion and extension bilaterally. The remainder of the exam was unremarkable. On initial laboratory assessment, white blood cell count was 11.9 k/mm3 (normal 4–10), total bilirubin 24.6 mg/dL (normal 0.1–1.2), direct bilirubin 13.0 mg/dL (normal 0.1–0.3 mg/dL), ALT 1053 U/L (normal <41), AST 2994 IU/L (normal 5–40), alkaline phosphatase 2893 IU/L (normal 40–129). Lipase, creatinine, and GFR were within normal limits. CK was elevated to 38,000 U/L (normal 39–308). The patient’s urine sample was tea-coloured on gross inspection. Urinalysis was performed although of limited utility as the pH, leukocyte esterase, nitrites, protein, glucose, ketone, bilirubin, and blood values were unable to be assessed due to interfering color. Regarding WBC and RBC counts, both returned at 0–2 (normal <2).

Given the elevation in CK, the patient’s statin was held, and he was started on aggressive fluid resuscitation. An abdominal CT scan showed a 3 cm obstructing pancreatic head mass with diffuse pancreatic, biliary, and gallbladder dilatation. Carbohydrate 19–9 antigens returned elevated at 8,782 U/mL (reference range 0–37 u/mL). Duodenal biopsy confirmed pancreatic adenocarcinoma. Given his significant bilateral lower extremity weakness, MRI lumbar spine was done to rule out metastasis. MRI revealed diffuse edema within the paraspinal and bilateral psoas muscle with associated patchy enhancement that was thought to represent sequel of myositis. No metastatic spinal cord compression was appreciated.

Despite early initiation of aggressive fluid resuscitation, the patient’s CK continued to rise. Given concern for inflammatory myositis, on hospital day 5 the patient was initiated on prednisone 80 mg/day. On hospital day 6, following initiation of steroids, his CK
2. Discussion

We present a case of newly diagnosed pancreatic cancer presenting with inflammatory myopathy and marked elevation in CK. We review the frequency of PM as a paraneoplastic syndrome, the association with pancreatic cancer, and the association with marked elevation in CK.

2.1. Definitions

DM and PM are both immune-mediated inflammatory myopathies that typically present with symmetric, proximal muscle weakness. The primary differentiating factor between the two entities is the skin involvement associated with DM. Both processes can occur as paraneoplastic syndromes associated with a new diagnosis of malignancy [1–3].

2.2. Epidemiology

The incidence of inflammatory myopathies ranges from 1.6 to 19 per million, with an estimated prevalence of 14 per 100,000 [4]. Women are more frequently affected than men [5]. The average age of those affected by PM and DM is 50–60 years [5]. The observed association between inflammatory myopathies and malignancy is more common in DM than PM and varies from 3% to 60% [6].

The association of DM as a paraneoplastic syndrome has been well reported. Hill et al. performed a pooled analysis of published literature from Sweden, Denmark, and Finland and noted that DM was associated with an increased risk of developing a wide array of cancers, including breast, ovarian, lung, pancreatic, stomach, colorectal, and non-Hodgkin lymphoma [7]. Since 1916, it has been speculated that patients with PM have a similarly increased risk of developing cancer. Cancers commonly associated with PM include breast [8–10], squamous cell lung cancer [11], adenocarcinoma of lung [12–14], bladder cancer, and Non-Hodgkin lymphoma [1,8,15]. Additionally, literature review reveals an isolated case of PM associated with colon cancer [16]. Based on literature review, inflammatory myopathies, such as PM, are rarely associated with pancreatic neoplasms [7].

2.3. Clinical presentation

Pancreatic cancer-associated myopathy remains a rare syndrome. A meta-analysis of 20 studies performed by Yang et al. reviewed cancer-associated myopathies occurring in various malignancies and only 3/20 studies implicated pancreatic cancer [17]. Of the 95 PM patients reviewed by Hill et al. who developed cancer, there was only one case of pancreatic cancer [7]. The other two studies had 33 and 43 patients, respectively, and each had just one case of pancreatic cancer [18,19]. Kida et al., Syrios et al., Siddiqui et al., and Amroun et al. have also reported isolated cases of pancreatic adenocarcinoma associated with PM as described in Table 1 [15,20–22]. Two of four patients received treatment with Gemcitabine, a known cause of drug-induced myopathy [23,24]. Chemotherapeutic agents typically cause myopathies to sites previously exposed to radiation, but gemcitabine is unique in that it can cause myopathies in radiation-naive patients [25]. Therefore, administration of chemotherapeutic gemcitabine further complicates diagnosis of cancer-associated PM or myopathy.

PM characteristically affects the proximal muscles of the upper and lower extremities. Lumbar MRI in our case revealed edema within the paraspinal and psoas muscles, suggesting myopathy is consistent with PM affecting these muscle groups (Figures 1 and 2). While imaging in PM is more commonly performed in the proximal lower extremities, specifically the thighs, whole-body imaging with PET or MRI suggests that involvement of paraspinal and psoas muscle groups is not uncommon. Whole-body MRI performed on 129 patients with PM or DM revealed muscle inflammation in 105 patients. Inflammation of pelvic and lumbar musculature was noted in 94 and 85 patients respectively [26]. O’Connell et al. reported involvement of the psoas in four out of seven patients with PM reviewed. [27] Involvement of paraspinal and psoas musculature is likely rarely reported due to conventional imaging practices. Our case demonstrates that paraspinal and psoas musculature may be implicated in paraneoplastic PM.

2.4. Diagnosis and pathology

DM or PM are typically diagnosed with muscle biopsy findings. DM can also be diagnosed by skin biopsy or by
Table 1. Cases of pancreatic carcinoma associated polymyositis and myopathy.

| Case          | Kida et al.\(^{[20]}\) | Syrios et al.\(^{[15]}\) | Siddiqui et al.\(^{[21]}\) | Amroun et al.\(^{[22]}\) | Padniewski et al., present case |
|---------------|------------------------|--------------------------|---------------------------|--------------------------|---------------------------------|
| Publication year | 2007                  | 2011                    | 2011                      | 2012                     | 2020                             |
| Cancer type   | pancreatic adenocarcinoma | pancreatic adenocarcinoma | invasive papillary adenocarcinoma | infiltrating ductal pancreatic adenocarcinoma | pancreatic adenocarcinoma |
| Diagnostic tools | CPK and biopsy      | CPK, electromyography and biopsy | CPK and biopsy | CPK and biopsy | CPK, MRI, no confirmatory biopsy performed, presumed polymyositis unable to be confirmed |
| Gemcitabine use | No                           | Yes                      | Yes                       | No                       | Yes, later in course             |
| Management    | Prednisolone, fluorouracil, radiotherapy | Glucocorticoids, gemcitabine, erlotinib | Prednisone, surgical resection | Surgical resection, gemcitabine | Prednisone, FOLFOX followed by gemcitabine |
| Additional findings | Late-stage carcinoma | -                        | -                         | -                        | Myopathy developed prior to gemcitabine |
| Outcome       | Died 4 years after diagnosis | Remission for 6 months, then relapse | Remission               | Remission | Gemcitabine trial, death 1 month later |

Figure 1. MRI of patient’s lumbar spine. T2 image with solid arrows showing edema of paraspinal muscles. Outlined arrows indicated psoas muscles, which are non-edematous.

Figure 2. MRI of patient’s lumbar spine. T1 with contrast image with arrows indicating areas of enhancement in lumbar paraspinal muscles.
the combination of proximal muscle weakness and the presence of a characteristic rash. EMG and auto-
antibodies may further support the diagnosis of PM or DM but are not required for diagnosis.

Our patient was diagnosed with paraneoplastic myopathy because of symmetrical, proximal muscle weak-
ness, elevated CK level, imaging findings, and response to steroids in the setting of a new pancreatic adenocarci-
noma diagnosis. While a muscle biopsy would have solid-
dified the diagnosis of paraneoplastic myopathy, this was unfortunately not obtained.

Statin-induced myopathy (SIM) was considered on the initial differential and statin therapy was discontinued
upon arrival at the hospital. SIM was felt to be less likely, as the symptoms did not start upon initiation and per-
sisted despite discontinuation of the statin. Immune mediated necrotizing myopathy (IMNM) was also con-
sidered. IMNM typically presents as a subacute progressive myopathy with presence of HMGCR autoantibodies
[28]. Statin therapy can rarely result in immune mediated necrotizing myopathy. Although less likely, without a
biopsy and antibody panel, we cannot definitively rule this out. To further elucidate similar cases, muscle biopsy,
auto-antibodies and electromyography studies should be pursued. However, the new diagnosis of pancreatic can-
cer, lack of rash to support the diagnosis of DM, and response to steroids make paraneoplastic myopathy the most likely etiology in our case.

2.5. Treatment

Paraneoplastic PM is treated similarly to idiopathic PM. Both conditions are typically treated with high-dose cor-
ticosteroids followed by a transition to a steroid-sparing agent such as methotrexate or azathioprine [29,29].
Response to therapy for DM and PM ranges from weeks to months [29,29,30]. Our patient had a rather prompt response to therapy, which is not typical for DM or PM but has been reported in the literature with myopathies [30–32].

It is notable that paraneoplastic PM is less likely to respond to steroid therapy and lack of expected response to steroids should prompt evaluation of underlying malignancy. Treatment of the associated cancer results in improvement of myositis [6,33]. Paraneoplastic PM significantly worsens the overall prognosis of recovery of muscle function as compared to other cases of PM [1,34–36].

3. Conclusion

This case exemplifies the importance of maintaining clinical suspicion of underlying malignancies in patients presenting with symptoms of inflammatory myopathies, such as DM and PM. It is crucial to perform thorough evaluation of malignancy as early diagnosis and treatment may improve prognosis specifically in cases of DM and PM. Concurrent rhabdomyolysis is also important to consider when diagnosing PM. Chemotherapeutic agents, such as gemcitabine, have been implicated in myopathies and should be noted on medication survey in addition to statin therapies. Atypical muscle group involvement does not rule out PM. Ultimately, muscle biopsy, serum antibodies, and EMGs should be used in making a definitive diagnosis of paraneoplastic myopathy, PM, and DM.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Jessica Joanne Padniewski http://orcid.org/0000-0002-8696-8615

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