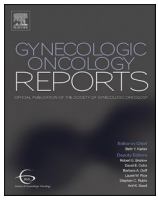
Gynecologic Oncology Reports 56 (2024) 101519

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor



Docetaxel induced myositis in the treatment of uterine Leiomyosarcoma: A case report and review of literature

Nourah Ibrahim [a,*], Alon D. Altman [b]

[a] Department of Obstetrics, Gynecology and Reproductive Sciences, University of Manitoba, Winnipeg, MB, Canada
[b] Department of Obstetrics, Gynecology and Reproductive Sciences, University of Manitoba, Winnipeg, MB, Canada

1. Introduction

The combination of Docetaxel and Gemcitabine are commonly used regiments for patients with uterine leiomyosarcoma, with proven efficacy (Maki et al., 2007). The main mechanism of action of Docetaxel is binding to microtubules and preventing their depolarization, thus inhibiting mitosis. The Taxanes (Paclitaxel and Docetaxel) are cell cycle specific in the M−phase.

Docetaxel is known to cause myelosuppression, peripheral neuropathy, fluid retention, myalgia and arthralgia (Rowinsky et al., 1993). However, severe acute myositis is a rare side effect with only a few reported cases (Rochigneux et al., 2018; Saini et al., 2015; Perel-Winkler et al., 2015; Ardavanis et al., 2005; Hughes and Stuart-Harris, 2005; Wongsaengsak et al., 2021; Thomas et al., 2020; Ishida et al., 2022; Sulkes et al., 2023) and none described in Gynecology Oncology cancers. We report a case of Docetaxel induced myositis in patient with uterine leiomyosarcoma.

2. Case report

This is a 51 year old lady who presented with transfusion dependent abnormal uterine bleeding. She is known to have Ehlers-Danlos Syndrome (EDS), Type 2 Diabetes Mellitus, Hypertension and Hypothyroidism. On imaging, a 15 week bulky uterus was noted. An endometrial biopsy was negative for hyperplasia or malignancy. Her bleeding was refractory to medical management and she consented to definitive surgical treatment with total abdominal hysterectomy and bilateral salpingo-opherectomy. The surgery and postoperative period were uncomplicated.

Final gynecology pathology showed a morphology and immunohistochemical staining consistent with a uterine leiomyosarcoma (LMS), measuring 4.7x3.0x2.7 cm, with no evidence of LVSI. The specimen showed high grade spindle cell neoplasm with necrosis, markedly increased mitotic index and marked cytologic atypia. Due to these concerning pathological features, the decision of the Tumor Board was four cycles of adjuvant chemotherapy with Gemcitabine and Docetaxel for her Stage 1A uterine leiomyosarcoma. During her first cycle, the patient had subjective fever and arthralgia for 48 h. A comprehensive infectious workup including viral swabs, blood and urine cultures, chest x-ray and a detailed history was performed to identify potential sources of infection, all of which yielded negative results. Although the patient reported a subjective fever, no objective fever was documented.

It was hypothesized that this reaction could be due to either edema associated with docetaxel or possible delayed allergic reaction. Another likely cause could be due to gemcitabine induced flu like syndrome, a recognized side effect reported in 19 % of patients (Martin et al., 1996). Higher frequencies are noted with more intense dosing (Martin et al., 1996). Symptoms include fever, chills, and musculoskeletal pain. These symptoms typically occur within hours of administration and are short lived. The patient's symptoms were effectively managed with steroids for two days and did not recur in later cycles.

Ten days after her 4th and final cycle of chemotherapy, she presented to the emergency department with a 1-week history of myalgia, significant proximal muscle pain, swelling and weakness in bother her upper and lower limbs bilaterally. Though the patient has a history of musculoskeletal pain related to her history of Ehlers Danlos Syndrome (EDS), she clearly noted that this pain was more severe, more pronounced in both thighs and worsens with movement. The patient denied joint pain or symptoms of viral illness preceding her presentation. On physical examination, there were no rashes or skin lesions. However, significant non pitting edema in both upper and lower limbs with symmetric proximal muscle pain and weakness in all limbs (Power 4/5) was noted. The remainder of the neurological exam was normal. Laboratory tests revealed elevated creatinine kinase (CK) 1195 IU/L, Myoglobin 810 ug/L and C reactive protein of 169 mg/L. Anti-nuclear antibody, double stranded DNA antibody, anti-smith antibody, scleroderma antibody, and other myositis specific and associated antibodies (anti-JO1, Sm, RNP/Sm, Ribosomal P, Centromere B, Chromatin) were

* Corresponding author at: Cancer Care Manitoba Foundation 1160-675 McDermot, Ave Winnipeg, MB R3E 0V9, Canada.
E-mail addresses: drnourahibrahim@gmail.com (N. Ibrahim), aaltman@cancercare.mb.ca (A.D. Altman).

https://doi.org/10.1016/j.gore.2024.101519
Received 23 August 2024; Received in revised form 27 September 2024; Accepted 28 September 2024
Available online 30 September 2024

all negative.

Magnetic resonance imaging showed symmetric intramuscular edema within the rectus femoris, sartorius and tensor fascia late muscles and right triceps muscles.

She was diagnosed with acute Docetaxel induced myositis (DIM) due to the temporal relationship, the clinical, biochemical and imaging findings. Rheumatology specialists were involved in the evaluation and management of this patients condition and treatment was initiated with opioid analgesics and high dose prednisone, 50 mg PO daily for 1 week, followed by a gradual taper, 25 mg PO for 5 days then 10 mg for 5 days then discontinued. Her symptoms slowly improved and serum CK and myoglobin levels gradually normalized. During her admission, she worked closely with physiotherapy and occupational therapy to improve her mobility. She was discharged after 2 weeks and continued to work with physiotherapy as an outpatient. She returned to her baseline after 3 months.

3. Discussion

We report on a case of DIM shortly after completing four cycles of chemotherapy for the treatment of uterine leiomyosarcoma. The patient presented with severe symmetric proximal muscle pain and weakness in all limbs with clinical, laboratory and imaging results supporting a diagnosis of acute myositis related to docetaxel.

DIM has been described in a few case reports with treatment of breast, prostate and non small cell lung cancer (Rochigneux et al., 2018; Saini et al., 2015; Perel-Winkler et al., 2015; Ardavanis et al., 2005; Hughes and Stuart-Harris, 2005; Wongsaengsak et al., 2021; Thomas et al., 2020; Ishida et al., 2022; Sulkes et al., 2023). However, to the best of our knowledge, acute myositis related to docetaxel treatment in gynecology oncology cancer has not been reported.

The exact mechanism of taxane induced myositis is not known. One proposed hypothesis is a transient increase in cytokine levels because of systemic leakage of proteins into the interstitial space. This could cause infiltration of immune cells into the muscle tissue (Wongsaengsak et al., 2021). Another proposed theory is the direct toxic effect of Docetaxel on muscle tissue (Wongsaengsak et al., 2021).

Our literature review (Table 1) demonstrated that there are certain characteristics that are common among DIM patients. First myositis mostly developed after 30–90 days of docetaxel exposure. The commonly affected area was the bilateral proximal muscles of the lower limb. Up to 70 % of patients had type 2 diabetes mellitus, a possible predisposing factor (Wongsaengsak et al., 2021). Similar to our case, the majority of published cases reached a diagnosis with use of clinical, laboratory and radiological findings. Treatment was similar in all patients with discontinuation of docetaxel and symptoms management with high dose steroids, except for 1 case, due to uncontrolled diabetes (Rochigneux et al., 2018).

The diagnosis of DIM requires establishing a temporal relationship between chemotherapy regimen initiation and symptom onset. As shown in other studies (Table 1), a comprehensive clinical evaluation is imperative, in addition to biochemical and imaging evidence. In this case, the timing of symptoms onset relative to chemotherapy, elevated muscle enzymes (such as CK and CRP) and MRI findings of intramuscular edema, provided sufficient evidence for diagnosis. While the MRI showed edema, this was indicative of localized muscle inflammation,

Table 1
Case Reports of Docetaxel Induced Myositis.

Author/year publication	Age/ Sex M/F	Co–morbidity	Cancer type	Chemotherapy regimen	Dose of Docetaxel	Myositis location	Onset	Max CK U/L	Myositis duration (days)	Myositis treatment
Our case	51/F	T2DM HypoT4 EDS HTN	Stage 1A Uterine Leiomyosarcoma	Docetaxel, Gemcitabine	75 mg/m2	Bilateral upper arm and thighs	1 week after 4th cycle	1195	14	Opioid analgesia Steroids
Sulkes et al./ 2023	62/F	DM HTN	Stage 2 Breast Cancer	Docetaxel Cyclophosphamide	75 mg/m2	Bilateral thighs	4 days after 2nd cycle	3122	NA	Steroids
Ishida et al./ 2022	66/ M	T2DM HTN DLP	Stage 4 Lung Cancer	Docetaxel	60 mg/m2	Bilateral thighs	2 weeks after 2nd cycle	2515	38	Steroids
Wongsaengsak et al./ 2021	49/F	T2DM	Stage 2 Breast Ca	Docetaxel, Carboplatin, Trastuzumab, Pertuzumab	75 mg/m2	Bilateral thighs	1 week after 3rd cycle.	1018	6	Opioid analgesia and Steroids
Thomas et al./ 2020	72/F	None	Invasive duct breast Ca	Docetaxel, Cyclophosphamide	NA	Bilateral thighs	After 3rd cycle	NA	NA	Steroids
Rochigneux et al./ 2018	52/ M	T2DM	Stage 4 Prostate	Docetaxel	75 mg/m2	Bilateral thighs	1 week after 2nd cycle	3200	60	Opioids *(No Steroids due to uncontrolled diabetes)*
Saini et al. /2015	62/F	T2DM HTN	Stage 4 Breast Ca	Docetaxel, Carboplatin	NA	Bilateral thighs	After 2nd cycle	1558	7	Opioid analgesia Steroids
Perel-Winkler et al./ 2015	65/F	HTN DLP Seizure CAD PAD	Breast Ca unknown stage	Docetaxel, Cyclophosphamide	75 mg/m2	Right thigh	8 days after 2nd cycle	341	5	Steroids
Ardavanis et al./2005	57/ M	None	Stage 4 NSCLS	Docetaxel, Gemcitabine	100 mg/ m2	Bilateral thighs	1 week after 4th cycle	Twice normal	30	Steroids Diuretics
Hughes et al./ 2005	47/F	T2DM HTN	Stage 4 Breast Ca	Docetaxel, Epirubicin, Cyclophosphamide	100 mg/ m2	Bilateral thighs Bilateral feet	4–9 days after 1st cycle	4558	6	Opioid, non-opioid analgesia, Steroids

Abbreviation: T2DM: Type 2 diabetes mellitus; EDS: Ehler Danlos Syndrome; HTN: Hypertension; PAD: Peripheral arterial disease; DLP: Dyslipidemia; CAD: Coronary artery disease; HypoT4: Hypothyroidism; NA: not available.

differing from the generalized edema typically associated with docetaxel (Perel-Winkler et al., 2015; Ishida et al., 2022).

A muscle biopsy was performed in only two cases (Saini et al., 2015; Thomas et al., 2020). Whether a biopsy is warranted depends on the differential diagnosis and clinical presentation. Similar conditions such as dermatomyositis and polymyositis can often be ruled out without the need for biopsy as these conditions are associated with classic skin manifestation and earlier onset of muscle pathology, with symptoms improving with treatment (Ishida et al., 2022). Sensorimotor polyneuropathy can occur as a paraneoplastic syndrome or a side effect of chemotherapy (Perel-Winkler et al., 2015; Sulkes et al., 2023). In chemotherapy related cases, symptoms typically present progressively, muscle enzyme levels remain normal, and swelling is not commonly observed (Perel-Winkler et al., 2015). Diabetic myonecorosis, another potential diagnosis, is typically characterized with normal white cell count and CPK levels, but with elevation in ESR (Wongsaengsak et al., 2021). Additionally MRI findings include hyperintense signals on T2 weighted images and significant edema (Schulze et al., 2009). Although statin induced myopathy is another rare but possible cause, a thorough history can distinguish if a patient is at risk or not (Ishida et al., 2022).

Nonetheless, a biopsy is warranted, if the suspected condition of DIM does not improve with treatment or if distinguishing between condition such as diabetic myonecrosis or statin induced myopathy is challenging.

Most symptoms of DIM appear after multiple cycles of chemotherapy (Table 1). However, if myositis occurs early then treatment adjustments might need to be considered such as modifying the dose or schedule of docetaxel to mitigate the risk of exacerbating muscle inflammation and to provide early therapeutic benefit. If myositis is severe or persistent then doxorubicin may be used as an alternative chemotherapeutic regiment (Menon et al., 2024). The decision will depend on the efficacy and tolerability of alternative agents. Tumor Board consultation would be crucial to make informed decisions about continuing or modifying treatment plans for such cases.

A multidisciplinary approach with early involvement of physiotherapy and occupational therapy should be implemented to manage symptoms and improve mobility. This support should be continued throughout the treatment and recovery period. Nutritional support would also play a role in recover and in maintaining muscle health during chemotherapy.

It is worth noting that similar associations have been observed with Docetaxel and radiation treatment. Radiation recall myositis (RRM) is a rare inflammatory reaction in previously irradiated muscles, triggered by the administration of certain chemotherapy agents. Docetaxel has been associated with this phenomenon, causing pain, swelling and edema in irradiated areas after chemotherapy (Üçüncü Kefeli and Aksu, 2022). While RRM is more commonly linked to gemcitabine, recognizing docetaxel as a potential cause is crucial for early diagnosis and management, typically involving corticosteroids and anti-inflammatory drugs to alleviate symptoms (Üçüncü Kefeli and Aksu, 2022).

4. Conclusion

As Gynecological Oncologists, who frequently prescribe docetaxel, it is imperative to identify this rare but serious side effect so that effective early and long term management could be provided appropriately. Our case expands on the available literature that describes docetaxel induced myositis in other types of cancer. The reporting of these rare side effects in the literature will shed more light on potential risks of this unusual complication. Clarifying the exact pathophysiological mechanism of docetaxel induced myositis should be the focus of further research to help early recognition and management. A multi disciplinary approach with internists, rheumatology physicians, radiologists, and physiotherapists is essential.

- Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Financial Disclosure

None reported.

CRediT authorship contribution statement

Nourah Ibrahim: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation. **Alon D. Altman:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Ardavanis, A.S., Ioannidis, G.N., Rigatos, G.A., 2005. Acute myopathy in a patient with lung adenocarcinoma treated with gemcitabine and docetaxel. Anticancer Res. 1B, 523–525. PMID: 15816622.

Hughes, B.G., Stuart-Harris, R., 2005. Docetaxel-induced myositis: report of a novel side-effect. Intern. Med. J. 6, 369–370. https://doi.org/10.1111/j.1445-5994.2005.00846.x. PMID: 15892769.

Ishida, A., Ushio, A., Hashimoto, M., Ishii, S., Naka, G., Iikura, M., Izumi, S., Hojo, M., Sugiyama, H., 2022. A rare case of docetaxel-induced myositis in a patient with a lung adenocarcinoma. Thorac. Cancer 14, 2075–2077. https://doi.org/10.1111/1759-7714.14480. Epub 2022 May 20. PMID: 35595502; PMCID: PMC9284182.

Maki, R.G., Wathen, J.K., Patel, S.R., Priebat, D.A., Okuno, S.H., Samuels, B., Fanucchi, M., Harmon, D.C., Schuetze, S.M., Reinke, D., Thall, P.F., Benjamin, R.S., Baker, L.H., Hensley, M.L., 2007. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J. Clin. Oncol. 25 (19), 2755–2763. https://doi.org/10.1200/JCO.2006.10.4117. Erratum. In: J Clin Oncol. 2007 25(24):3790 PMID: 17602081.

Martin, C., Lund, B., Anderson, H., Thatcher, N., 1996. Gemcitabine: once-weekly schedule active and better tolerated than twice-weekly schedule. Anticancer Drugs 7 (3), 351–357. PMID: 8792011.

Menon, G., Mangla, A., Leiomyosarcoma, Y.U., 2024. StatPearls [internet]. StatPearls Publishing, Treasure Island (FL). PMID: 31869131.

Perel-Winkler, A., Belokovskaya, R., Amigues, I., Larusso, M., Hussain, N., 2015. A case of docetaxel induced myositis and review of the literature. Case Rep. Rheumatol. https://doi.org/10.1155/2015/795242. Epub 2015 PMID: 26257973; PMCID: PMC4519533.

Rochigneux, P., Schleinitz, N., Ebbo, M., Aymonier, M., Pourroy, B., Boissier, R., Salas, S., Deville, J.L., 2018. Acute myositis: an unusual and severe side effect of docetaxel: a case report and literature review. Anticancer Drugs 5, 477–481. https://doi.org/10.1097/CAD.0000000000000620. PMID: 29561309.

Rowinsky, E.K., Chaudhry, V., Forastiere, A.A., Sartorius, S.E., Ettinger, D.S., Grochow, L.B., Lubejko, B.G., Cornblath, D.R., Donehower, R.C., 1993. Phase I and pharmacologic study of paclitaxel and cisplatin with granulocyte colony-stimulating factor: neuromuscular toxicity is dose-limiting. J. Clin. Oncol. 10, 2010–2020. https://doi.org/10.1200/JCO.1993.11.10.2010. PMID: 7692001.

Saini, R., Chandragouda, D., Talwar, V., Rajpurohit, S., 2015. Grade IV myositis: a rare complication of docetaxel. J. Cancer Res. Ther. 3, 664. https://doi.org/10.4103/0973-1482.144361. PMID: 26458695.

Schulze, M., Kötter, I., Ernemann, U., Fenchel, M., Tzaribatchev, N., Claussen, C.D., Horger, M., 2009. MRI findings in inflammatory muscle diseases and their noninflammatory mimics. AJR Am. J. Roentgenol. 192 (6), 1708–1716. https://doi.org/10.2214/AJR.08.1764. PMID: 19457839.

Sulkes, A., Reinhorn, D., Cohen, T., Peysakhovich, T., Neiman, V., Brenner, B., 2023. Docetaxel-induced acute myositis. Isr. Med. Assoc. J. 1, 75–76. PMID: 36718745.

Thomas, J., Warrier, A., Kachare, N., 2020. Docetaxel-induced myositis. J. Clin. Rheumatol. 3. https://doi.org/10.1097/RHU.0000000000000888. PMID: 30148754 e62-e63.

Üçüncü Kefeli, A., Aksu, B., 2022. Docetaxel induces radiation recall myositis: a case report. Exp. Ther. Med. 24 (2), 516. https://doi.org/10.3892/etm.2022.11443. PMID: 35837073; PMCID: PMC9257963.

Wongsaengsak, S., Quirch, M., Ball, S., Sultan, A., Jahan, N., Elmassry, M., Rehman, S., 2021. Docetaxel-induced acute myositis: a case report with review of literature. J. Chemother. 2, 116–121. https://doi.org/10.1080/1120009X.2020.1785740. Epub 2020 Jul 3 PMID: 32619151.