Extravasation of Oxaliplatin into the Mediastinum: A Case Report and Review of the Literature

Roberto A. Leon-Ferre, MD[1]
Taher B. Abu Hejleh, MBBS[2]
Thorvardur R. Halfdanarson, MD[2]

[1]Department of Internal Medicine, [2]Division of Hematology, Oncology & Blood and Marrow Transplantation, University of Iowa Hospitals and Clinics, Iowa City, Iowa

Introduction

Oxaliplatin, a platinum-based drug that is typically part of the FOLFOX chemotherapy regimen (folinic acid, fluorouracil, and oxaliplatin) used in colorectal cancer, was initially described as a non-vesicant. Subsequent case reports of oxaliplatin extravasation, however, described local tissue inflammation and necrosis, which led to its reclassification as an irritant or a low-risk vesicant.[1]

In reviewing the literature, we identified 6 published reports describing a total of 16 patients that suffered oxaliplatin extravasation, in addition to 9 patients identified in the pre- and post-marketing surveillance of oxaliplatin.[1-7] All published cases involved extravasation into the subcutaneous tissues of the upper extremities or the breast, either through a peripheral vein (19 cases) or via a central catheter (6 cases). Most patients experienced mild tissue inflammation, with few cases resulting in severe reactions and tissue necrosis. Here, we report a case of accidental oxaliplatin infusion into the mediastinum through a central venous catheter. To our knowledge, no similar cases have been reported in the literature.

Case Report

An 87-year-old man with poorly differentiated stage IV squamous cell carcinoma (SCC) of the esophagus causing severe dysphagia was initially treated with concurrent chemoradiation that included paclitaxel, carboplatin, and 50.4 Gy of radiation therapy. Post-treatment positron emission tomography (PET)/computed tomography (CT) showed complete response. A repeat CT scan after 4 months, however, revealed new lung nodules that raised concerns of metastasis. An upper endoscopy was performed and revealed a circumferential esophageal mass, with biopsies confirming SCC relapse.

A decision was made to start the patient on FOLFOX. A central venous catheter (subcutaneous injection port) was placed in the left subclavian vein. The patient received the first cycle of FOLFOX without complications. Near the end of the second cycle, he reported mild chest discomfort that resolved spontaneously. During the third cycle, approximately 1 hour after the initiation of oxaliplatin, he experienced shortness of breath and severe mid-chest pain (10 on a 0–10 pain severity scale). The infusion was immediately stopped, and the patient was sent to the emergency room. On physical examination, he was afebrile and hemodynamically stable. Heart and lung examinations were unremarkable. The skin overlying the port did not show erythema and was not tender. Electrocardiography (EKG) and cardiac enzymes were unremarkable. Laboratory workup revealed no leukocytosis. A CT angiogram was performed and ruled out pulmonary embolism, but revealed that the central venous catheter tip was extravascular and resided in the anterior mediastinum, ventral to the ascending thoracic aorta (Figure 1). It had entered the left innominate vein and perforated it 2 cm proximal to the junction with the superior vena cava. There was air and fluid in the mediastinum, as well as bilateral pleural effusions and new ground-glass opacity in the right upper lobe adjacent to the catheter tip. The latter was suspected to represent pneumonitis.

The patient was admitted to our oncology service and started empirically on intravenous (IV) antibiotics for presumed mediastinitis. Pain control was achieved with morphine. Because he remained afebrile, reported no systemic symptoms, and had no increase in the white blood cell count, antibiotics were discontinued the next day. In the subsequent 24 hours, the patient's chest pain

Address correspondence to:
Roberto A. Leon-Ferre, MD, Department of Internal Medicine, University of Iowa Hospitals and Clinics, 200 Hawkins Dr, Ste C310, Iowa City, IA 52242-1007; Phone: 319-356-1616; Fax: 319-384-8955; E-mail: roberto-leon-ferre@uiowa.edu.

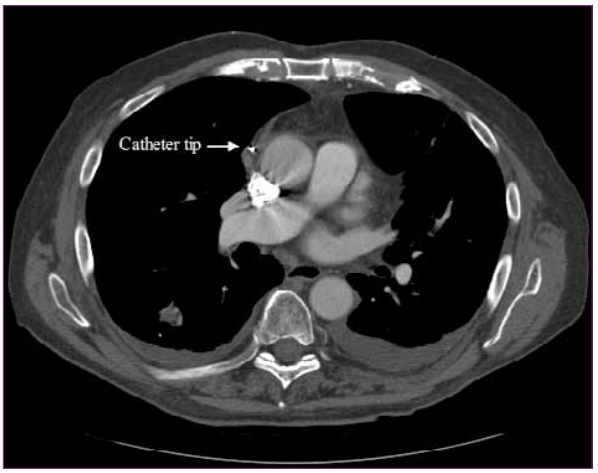

Figure 1. Catheter tip shown to be extravascular, in the mediastinum. Bilateral pleural effusions are also seen.

and shortness of breath almost resolved. The port was removed, and the patient was later discharged home. On week 1 of follow-up, the patient reported only minimal shortness of breath and pleuritic chest pain on deep inspiration. A prominent pleural rub was noted on auscultation. On week 2 of follow-up, a new port was placed, and he resumed chemotherapy uneventfully. On week 4 of follow-up, a repeat CT scan showed a decrease in the size of the pleural effusions and stable metastatic disease.

Discussion

Chemotherapy extravasation, although infrequent, is an iatrogenic adverse event that has the potential to lead to significant morbidity in cancer patients. It is estimated to occur in 0.1–6% of all peripheral intravenous infusions, and in approximately 3% of infusions through central venous access ports.[8,9] Oxaliplatin extravasation has been described in approximately 25 patients. All the cases reported, including the few that occurred while using central venous catheters, involved the soft tissues of either the upper extremities or the breasts.[2-7] Here, we describe for the first time an accidental oxaliplatin infusion into the mediastinum. Since oxaliplatin was approved, there has been no definitive answer to whether it should be considered a vesicant or non-vesicant.[1-4] In the reported cases, extravasation of oxaliplatin has been characterized by local pain, edema, and erythema that may resemble cellulitis or erysipelas.[3,6] A few necrotic-like reactions have been reported,[2,3,5] with associated skin and subcutaneous tissue induration and sclerosis, muscle fibrosis, and subsequent decreased range of motion of the extremity. Fortunately, the functional joint impairment resolved almost completely in all the patients within 1–4 months with physical therapy.[2-4]

Since all published cases of oxaliplatin extravasation involved the extremities or the breasts, it is not known what type of damage, if any, is to be expected with intrathoracic extravasation. In a review of intrathoracic extravasation of antineoplastic agents,[10] the authors identified reports involving 4 vesicant drugs (vincristine, vinblastine, daunorubicin, and epirubicin) and 1 irritant drug (fluorouracil). The most common complications included chest pain, fever, dyspnea, cough, arrhythmias, and pleural and pericardial effusions. There was also 1 case of upper lung lobe fibrosis in a patient with fluorouracil extravasation.[10] Most patients with intrathoracic extravasation of vesicants were managed conservatively, although 1 patient underwent mediastinal irrigation.[11] There were no fatal outcomes, and all patients recovered with minimal sequelae that included interstitial lung changes, costophrenic adhesions, and mild esophageal dysfunction.

Information on the management of oxaliplatin extravasation is limited. Cases of extravasation into the subcutaneous tissues have been managed with immediate discontinuation of the infusion and application of cold packs. It has been feared that the latter could precipitate sensory neuropathy; however, this was not reported as a complication in any of the cases treated with this method.[1] In addition, patients were managed with nonsteroidal anti-inflammatory drugs (oral or topical), heparinoid creams,[4,7] and opioids. Some patients received antibiotics, especially when the skin changes resembled cellulitis.[2-4,6] Steroids were used in 3 patients with an apparent improvement of symptoms.[6,7] Surgery was recommended in 1 case with significant muscle necrosis, but the patient declined and still had an almost complete recovery within 4 months.[3] The authors concluded that, even with severe tissue damage, a trial of conservative management might be reasonable.

In conclusion, intramediastinal oxaliplatin extravasation is an uncommon event that, to the best of our knowledge, has never been reported in the literature before. The increased use of central venous catheters to infuse this drug may lead to more cases like this in the future. Although severe tissue inflammation and necrosis has been reported in cases involving the soft tissues, it seems that intramediastinal oxaliplatin extravasation can be managed with close observation and symptomatic treatment alone. Individual cases, however, may require a more aggressive approach. Given that information regarding the management of this complication is still limited, prevention is of paramount importance. Difficulty drawing blood from a port might indicate that the catheter is extravascular. When doubts exist, proper catheter positioning should be confirmed prior to its use.

References

1. de Lemos ML, Walisser S. Management of extravasation of oxaliplatin. *J Oncol Pharm Pract*. 2005;11:159-162.
2. Baur M, Kienzer HR, Rath T, Dittrich C. Extravasation of oxaliplatin (Eloxatin((R))) - Clinical Course. *Onkologie*. 2000;23:468-471.
3. Kennedy JG, Donahue JP, Hoang B, Boland PJ. Vesicant characteristics of oxaliplatin following antecubital extravasation. *Clin Oncol (R Coll Radiol)*. 2003;15:237-239.
4. Foo KF, Michael M, Toner G, Zalcberg J. A case report of oxaliplatin extravasation. *Ann Oncol*. 2003;14:961-962.
5. Eckert R, Maier KP. Necrotizing panniculitis after extravasation of oxaliplatin. *Ann Oncol*. 2002;13(suppl 5): Abstract 103.
6. Kretzschmar A, Pink D, Thuss-Patience P, et al. Extravasations of oxaliplatin. *J Clin Oncol*. 2003;21:4068.
7. Pericay C, Lopez A, Soler JR, et al. Extravasation of oxaliplatin: an infrequent and irritant toxicity. *Clin Transl Oncol*. 2009;11:114-116.
8. Langer SW. Extravasation of chemotherapy. *Curr Oncol Rep*. 2010;12:242-246.
9. Lemmers NW, Gels ME, Sleijfer DT, et al. Complications of venous access ports in 132 patients with disseminated testicular cancer treated with polychemotherapy. *J Clin Oncol*. 1996;14:2916-2922.
10. Bozkurt AK, Uzel B, Akman C, et al. Intrathoracic extravasation of antineoplastic agents: case report and systematic review. *Am J Clin Oncol*. 2003;26:121-123.
11. Duhrsen U, Heinrichs V, Beecken WD, et al. Local and systemic sequelae of mediastinal daunorubicin extravasation in a patient with acute myelomonocytic leukemia. *Ann Oncol*. 1997;8:1167-1168.

Review

Mediastinal Extravasation of Oxaliplatin

Carles Pericay Pijaume, MD, and Eugeni Saigí, MD

Department of Medical Oncology, Corporació Sanitària Parc Taulí, Sabadell, Barcelona, Spain

Discussion

Leon-Ferre and colleagues describe an interesting case of an 87-year-old man with a poorly differentiated stage IV squamous cell carcinoma of the esophagus, treated in the progression scenario with folinic acid, fluorouracil, and oxaliplatin (FOLFOX) chemotherapy.[1] This chemotherapy regimen is used primarily in patients with localized or resected metastatic colorectal adenocarcinoma.[2]

The administration of FOLFOX requires a central catheter in order to avoid hospitalization and to maintain an efficient method of chemotherapy administration, thereby avoiding extravasation of the drugs. Although it is difficult to give an accurate measurement of its incidence, extravasation has been reported to occur in 0.1–6% of cases, and in approximately 3% of infusions through central venous access ports.[3] However, when chemotherapy is administered in specialized care centers, the use of central catheters yields a seepage rate of nearly 0%.[3] Today, according to our institutional experience, the percentage of peripheral extravasations is less than 0.0001% in peripheral veins and 0% in central catheters. A central venous catheter contains a subcutaneously implanted reservoir for chemotherapy administration. The most common complications consist of wound dehiscence, infection, and thrombosis.[4] Only a few cases of oxaliplatin extravasation through a central venous access have been described to date, such as the detachment of the intravenous cannula and migration to the heart, with subsequent risk of cardiac perforation.[5] Bad channeling of the vena cava or the drilling of branches adjacent to it, as in the case presented, are other potential complications.

Oxaliplatin has been shown to be a non-vesicant drug, even in a case of extravasation through a central venous access of the highest dose (165 mg) reported to date.[6] The toxicity produced in the subcutaneous tissue resolved with appropriate therapeutic measures by approximately 6 months. Topical measures with nonsteroidal anti-inflammatory drugs and corticosteroids have been important in such cases.

Aside from isolated case reports, the literature on mediastinal extravasation of chemotherapy is rather scarce.[7] Until the publication of this case, there were no published data on mediastinal extravasation of oxaliplatin. The symptoms expressed by the patient were pain and shortness of breath, associated with radiologic images of pleural effusion. The patient received intravenous antibiotics for presumed mediastinitis and morphine for pain control. Symptoms improved significantly after 1 week. By week 2, chemotherapy resumed, and by week 4, a repeat computed tomography scan showed a decrease in the size of the pleural effusions and stable metastatic disease. This case report shows that appropriate management of mediastinal extravasation of oxaliplatin can lead to full recovery.

Address correspondence to:
Carles Pericay Pijaume, MD, E. Saigí Grau, Oncology Department, Corporació Sanitària Parc Taulí, Parc Taulí, s/n, ES-08208, Sabadell, Barcelona, Spain; E-mail: cpericay@gmail.com.

References

1. Leon-Ferre RA, Abu Hejleh TB, Halfdanarson TR. Extravasation of oxaliplatin into the mediastinum: a case report and review of the literature. *Clin Adv Hematol Oncol*. 2012;8:546-548.
2. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27:3109-3116.
3. Langer SW. Extravasation of chemotherapy. *Curr Oncol Rep*. 2010;12:242-246.
4. Chang YF, Lo AC, Tsai CH, et al. Higher complication risk of totally implantable venous access port systems in patients with advanced cancer - a single institution retrospective analysis. *Palliat Med*. November 2011 [Epub ahead of print].
5. Wang CC, Chen YW, Wu ET, et al. Identification and management of cardiac perforation from a double lumen catheter in an infant. *Paediatr Anaesth*. 2007;17:500-501.
6. Pericay C, López A, Soler JR, Bonfill T, Dotor E, Saigí E. Extravasation of oxaliplatin: an infrequent and irritant toxicity. *Clin Transl Oncol*. 2009;11:114-116.
7. Bozkurt AK, Uzel B, Akman C, Ozgüroğlu M, Molinas Mandel N. Intrathoracic extravasation of antineoplastic agents: case report and systematic review. *Am J Clin Oncol*. 2003;26:121-123.