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Research Article

Acute Pancreatitis Induced by Platinum Salts: A Case Report and Systematic Review

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ABSTRACT

Platinum salts are used in the treatment of various tumors and are associated with several adverse effects. Acute pancreatitis is a rare but life-threatening complication. We report a case of Drug-Induced Acute Pancreatitis (DIAP) due to cisplatin and present a systematic review focusing on clinical features and management strategies.

A systematic review was conducted using covidence, encompassing literature published from 1985 to 2024 that reported DIAP secondary to platinum salts.

Ultimately, seven studies were included, comprising six case reports and one case series, resulting in a total of 12 cases: Five due to cisplatin, six due to oxaliplatin, and one due to carboplatin. The recorded cases included seven instances of gastrointestinal cancer, as well as one case each of lung, ovarian, testicular, breast and cervical cancer. The average latency between the initiation of treatment and the onset of DIAP was 5.2 ± 2.17 days following chemotherapy.

The therapeutic decisions made included stopping chemotherapy entirely in three cases, continuing with the same drugs under strict monitoring in two cases, discontinuing only the platinum salt in four cases, and replacing it in one case.

This work underscores the importance of early recognition of rare chemotherapy-related complications such as pancreatitis.

Keywords: Drug-induced pancreatitis, Chemotherapy, Platinum salts, Lung cancer, Oxaliplatin, Carboplatin, Cisplatin

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide, with approximately 2 million diagnoses and 1.8 million deaths reported in 2020 (Thandra KC, *et al*., 2021). This high mortality rate is largely due to late diagnoses, often at advanced stages of the disease.

Cisplatin, a platinum-based chemotherapy drug, is commonly used to treat advanced lung cancer, particularly in combination with pemetrexed for adenocarcinoma (Jamieson ER and Lippard SJ, 1999).

However, cisplatin is associated with various toxicities, including gastrointestinal adverse effects. One serious side effect documented is DIAP, which has been linked to cisplatin use.

In this report, we present a case of DIAP caused by cisplatin and conduct a systematic review focusing on the role of platinum salts in the occurrence of DIAP.

MATERIALS AND METHODS

We present the case of a 61-years old retired firefighter with no history of smoking or alcohol use and a medical history of type 2 diabetes. In June 2024, patient was diagnosed with stage IIIc lung adenocarcinoma Tumor 3, Node 3, Metastasis 0 (T3N3M0) following several investigations. A chest Computed Tomography (CT) scan revealed a 6.2 cm solid mass in the right lower lobe (Fowler's segment), along with bilateral nodules and several enlarged right mediastinal lymph nodes.

Additional CT scans of the abdomen, pelvis and brain showed no metastases. Positron Emission Tomography (PET) imaging indicated a hyper metabolic tumor in the right lower lobe Standardized Uptake Value (SUV=12.4) and hyper metabolic lymph nodes on both sides (SUV=7-10). Bilateral parenchymal lesions exhibited low to moderate metabolic activity (SUV=2). Histopathological examination from a transthoracic biopsy confirmed a well-differentiated lung adenocarcinoma, with negative mutational analysis (Bramer WM, *et al*., 2017).

The multidisciplinary team decided to initiate sequential radio-chemotherapy with cisplatin 75 mg/m^2 and Pemetrexed 500 mg/m^2 every 21 days. 24 hours after the first chemotherapy cycle, the patient experienced upper abdominal pain radiating to the back, along with repeated episodes of vomiting and fever. Lipase levels were significantly elevated at 437 U/L (8 times the normal range). An abdominal ultrasound and blood lipid profile returned normal results. Potential causes of acute pancreatitis, such as alcoholism, gallstones, hypertriglyceridemia and biliary interventions, were ruled out. The patient was treated with intravenous fluids, antacids and analgesics. A follow-up CT scan confirmed the uncomplicated status of the pancreatitis. Given the absence of identifiable causes and the timing of symptoms, drug-induced pancreatitis was suspected.

After 10 days of treatment, the patient showed symptomatic improvement, with lipase levels decreasing from 437 to 242 U/L. A pharmacovigilance consultation evaluated the imputability of the drugs involved; their role could not be ruled out due to the compatible timing of symptoms and lack of alternative etiologies. Although cisplatin was classified as a class II drug associated with pancreatitis, the overall incidence of pemetrexed-induced pancreatitis was low. Consequently, it was decided to continue pemletrexed while excluding cisplatin from subsequent cycles and substituting it with carboplatin.

The patient received two cycles combining carboplatin and pemetrexed without any clinical or biological manifestations of pancreatitis observed. Throughout this challenging prognosis and the complications associated with chemotherapy, the patient maintained a perspective marked by hope and acceptance. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (*Table 1*).

Table 1: Summary of studies reporting Drug-Induced Acute Pancreatitis (DIAP) associated with platinum agents

Platinum agent	Associated molecules	Treated caancer	Age and gender	Dose	Latency	Pancreatic enzymes	Investigations	Therapeutic decision
Cisplatin	No	-	-	-	-	-	-	-
Cisplatin	Bleomycin, and vinblastine	Ovary cancer	24 years-old female	Every 21 days	7th day after the first cure	Lipase (368 U/L)	Abdominal and chest X-rays, liver and renal blood tests	Vinblastine ⇔Etoposide+ bleomycin
		Testicular cancer	20 years-old male	Every 21 days	6th day after the first cure	Amylase (117 U/L)	Abdominal ultrasound and blood tests	Keep the same molecules, relapse of DIAP
Cisplatin	Vindesine	-	Male	-	-	-	-	-
Cisplatin	Gemcitabine	Lung Cancer Stage VI	68 years-old female	Cisplatin 100 mg/m2 IV day I. Gemcitabine 1000 mg/m^2 IV days	2nd day of the first cure	-	-	-
Cisplatin	Etoposide	Cervical cancer	25 years-old, female	Cisplatin 25 mg/m2 and etoposide 100 mg/m^2	One week after the 6th cure	Lipase (163U/L)	-	Keep the radiotherapy only.
Carboplatin	Docétaxel and trastuzumab	Breast cancer stage IIA	60 years-old, female	-	3-4 days after the third cure	Amylase (1294U/L) lipase (954 U/L)	CT scan and blood tests	Keep trastuzumab only for 1 year
Oxaliplatin	5-Fluoro-uracile, folinic acid and bevacizumab	Gastric cancer stage IV	71 years-old, male	-	-	Amylase (226U/L) lipase (184 U/L)	Abdominal CT scan	The whole chemotherapy stopped
	Gemzar	Pancreatic adenocarcinoma stage IV	51 years-old, male	-	-	Amylase (327U/L) lipase (708 U/L)	Abdominal CT scan	Oxaliplatin was stopped, gemcitabine dose reduced
	Gemzar	Gall bladder adenocarcinoma stage IV	51 years-old, male	-	-	Amylase (55U/L) lipase (1800 U/L)	Abdominal CT scan	The whole chemotherapy stopped
	5-Fluoro-uracile, folinic acid and bevacizumab	Colon cancer stage IV	67 years-old, male	-	-	Lipase (139U/L)	Abdominal CT scan	Oxaliplatin stopped
	Gemzar	Pancreatic adenocarci-noma	67 years-old, female	-	-	Lipase (96 UI/L)	Abdominal CT scan	Oxaliplatin held, gemcitabine stopped
	Gemzar	Pancreatic adenocarci-noma	68 years-old, female	-	-	Amylase (188U/L) Lipase (289 U/L)	Abdominal CT scan	Oxaliplatin stopped, gemcitabine continued

Eligibility criteria

Retrospective case reports and case series reporting DIAP secondary to platinum salts were included in the review. No language restrictions were applied. Studies that were reviews or that treated DIAP related to substances other than platinum salts were excluded.

Data extraction

Two authors independently conducted the initial screening based on the inclusion criteria. In cases of discordant evaluations, a third author provided input to facilitate consensus. Covidence was used to remove duplicate studies and maintain records of identified and screened studies. A microsoft excel sheet was utilized to extract study characteristics such as type of study, year of publication, age, sex, platinum agent, associated chemotherapy molecules, latency, cancer type, level of pancreatic enzymes, investigations conducted and therapeutic decisions. If a study reported multiple patients, all patients from that study were pooled for analysis.

Outcome measures

The primary objective was to identify the total number of reported cases of DIAP caused by platinum salts. The secondary objectives were to describe the clinical characteristics of DIAP specific to each platinum salt.

Statistical analysis

Categorical variables were reported as frequencies with percentages, while continuous variables were presented as means with Standard Deviations (SD). Non-normally distributed data were reported as medians with Interquartile Ranges (IQR).

Risk of bias assessment

The Joanna Briggs Institute's (JBI) important appraisal checklists for case reports and case series were employed for risk of bias assessment. The checklist included 8 to 10 items; each item answered yes received a score of 1, while "no" received a score of 0. For case reports, quality scores of 2 or less, 3 to 5, and 6 or greater were considered low, moderate, and high quality, respectively. For case series and cohort studies, quality scores of 4 or less, 5 to 7, and 8 or greater were also categorized as low, moderate and high quality.

RESULTS AND DISCUSSION

A total of 436 studies were identified for analysis through various databases. Covidence excluded 37 duplicates, and two additional studies were identified manually. This left 397 studies that underwent an initial assessment based on their titles and abstracts. Among these, 126 studies were deemed irrelevant as they did not match the predefined criteria, and 41 studies were unobtainable for further evaluation. Subsequently, 231 studies progressed to a full-text review. During this phase, 223 studies were excluded based on the inclusion and exclusion criteria. Specifically, 142 studies were excluded because they addressed DIAP in general rather than specifically related to platinum salts (Nitsche CJ, *et al*., 2010; Badalov N, 2007).

Additionally, 57 studies included one of the platinum salts in their protocols but attributed pancreatitis to another associated molecule, while 23 lacked sufficient data. One study was excluded as it represented a systematic review on the same subject as ours. Ultimately, seven studies met the stringent criteria for inclusion in this systematic review.

DIAP is often treated as an exclusionary diagnosis and is relatively uncommon, accounting for only 0.1%-2% of all pancreatitis occurrences. The exact prevalence of DIAP remains unknown, as most instances have only been documented in individual cases.

The diagnosis of DIAP lacks specific clinical or laboratory diagnostic criteria. To make the diagnosis, upper abdominal pain, elevated amylase and/or lipase levels above the normal range and cross-sectional imaging findings are required. The drug-induced nature of pancreatitis should be considered only after ruling out other common causes, as more than 90% of cases are attributed to gallstones or alcohol consumption, with less common causes including hypertriglyceridemia, hypercalcemia, certain medications and infections. In all reported cases, blood tests and imaging studies such as CT scans or abdominal ultrasounds were conducted to eliminate these usual causes of acute pancreatitis (Szatmary P, *et al*., 2022).

Diagnosing DIAP hinges on recognizing the responsible drug, which can be challenging due to polymedication. Criteria for diagnosis include documented cases in the literature linking certain drugs to pancreatitis, the onset of pancreatitis following drug use, and resolution upon discontinuation of the drug. DIAP is often associated with didanosine (an anti-retroviral agent) and antibiotics such as tetracycline and sulfamethoxazole/trimethoprim; however, it is rarely linked to chemotherapy.

The latency between the initiation of drugs and the development of acute pancreatitis can be classified as short (less than 24 hours), intermediate (1-30 days), or long (more than 30 days). In our analysis, we found that the average latency was intermediate at 5.2 ± 2.17 days after chemotherapy initiation. Acute pancreatitis occurred in three cases after the first cycle of treatment, in one case after the third cycle, and in another case after the sixth cycle.

Primary outcomes

The seven included studies comprised six case reports and one case series, resulting in a total of 12 cases. Among these, there were five cases of DIAP due to cisplatin, six cases due to oxaliplatin, and one case due to carboplatin. The quality assessment of the case reports indicated that two studies were of low quality, while four studies were classified as high quality. The socio-demographic and clinical characteristics, as well as the outcomes related to DIAP from platinum salts, are summarized in *Table 1*.

The case reports quality assessment indicated that two studies were of low quality and four studies were of high quality. The socio-demographic, and clinical characteristics as well as the outcomes of the DIAP platinum salts are summarized in *Table 1*.

Secondary outcomes

For the 12 reported cases, the median age was 52 years (Range: 20-81 years), with a sex ratio of 1:1. We recorded six cases of gastrointestinal cancer, along with one case each of lung, ovarian, testicular, breast and cervical cancer. The average latency between the initiation of treatment and the development of DIAP was 5.2 ± 2.17 days after chemotherapy. Specifically, DIAP occurred in three cases after the first cycle of treatment, in one case after the third cycle and in another case after the sixth cycle (Trivedi CD and Pitchumoni CS, 2005).

The median lipase value among the cases was 289 U/L (Range: 96-1800 U/L), while the median amylase level was 207 U/L (Range: 55-1294 U/L). Investigations were conducted in all reported cases to exclude other common causes of pancreatitis, which included blood tests and imaging studies such as CT scans or abdominal ultrasounds.

Following the episode of DIAP, therapeutic decisions varied: Chemotherapy was stopped entirely in three cases, continued with the same drugs under strict monitoring in two cases, only the platinum salt was discontinued in four cases, and one case involved replacing the responsible platinum salt with another drug.

Causality assessment

Cisplatin: Cisplatin is one of the most commonly used chemical anticancer medications, effective in treating various tumors, including lung, breast, ovarian, cervical and head and neck cancers. It is categorized as a Class II medication linked to pancreatitis, with more than 10 but fewer than 20 documented occurrences of acute pancreatitis with or without

positive rechallenge. In another review, however, cisplatin was classified as class IV due to a weaker correlation with pancreatitis, primarily because there are few individual case reports in the literature establishing a direct link between cisplatin and the onset of acute pancreatitis.

The exact mechanisms by which cisplatin induces pancreatitis remain under investigation, but current understanding suggests that it may occur through several pathways, primarily involving oxidative stress and inflammation (Alhaddad O, *et al*., 2020).

Analysis of data from case reports indicates that the majority of cisplatin-induced acute pancreatitis cases were reported in young females, with an average age of 34 years (ranging from 20 to 68 years). Notably, only one case involved a pulmonary primary tumor in a 68-year-old female. Acute pancreatitis occurred after the first treatment cycle in three reported cases. The average latency between the initiation of cisplatin and the development of acute pancreatitis was approximately six days after treatment. In three cases where pancreatic enzyme levels were reported, the average lipase level was 265 U/L and the amylase level was 117 U/L. Investigations to rule out other diagnoses of acute pancreatitis were conducted in two cases and included abdominal ultrasound and blood tests (lipidic, liver and renal tests).

Therapeutic decisions following DIAP were documented in three cases: Cisplatin was discontinued in two instances while the same regimen was maintained in one case. Management of DIAP, like other types of acute pancreatitis, does not have a specific pharmacological treatment; instead, it primarily involves supportive care such as pain management, bowel rest, and hydration. In cases of infected necrosis, antibiotics may be indicated. The most important therapeutic decision is to interrupt the offending drug and substitute it with another anticancer agent that poses less risk (Mallory A and Kern F, 1988).

Carboplatin: Carboplatin is a chemotherapeutic agent used in the treatment of various cancers, primarily ovarian carcinoma, lung cancer, head and neck cancers, as well as endometrial, gastrointestinal, central nervous system and germ cell tumors. It is a cisplatin analog that exhibits significantly lower clinical nephrotoxicity. One notable case involved a 60-year-old caucasian woman with stage IIA HER2-positive breast cancer. Patient initiated an adjuvant chemotherapy regimen consisting of trastuzumab, carboplatin and docetaxel. The first two cycles of the regimen were well tolerated; however, the patient developed acute pancreatitis 3-4 days following the third and fourth cycles. The diagnosis was confirmed by elevated pancreatic enzymes (amylase at 1294 U/L and lipase at 954 U/L) and findings from an abdominal CT scan. All common causes of pancreatitis were ruled out, leading to the presumption that the patient condition was chemotherapy-induced. The patient continued on adjuvant trastuzumab alone for a full year without any recurrence of acute pancreatitis, while docetaxel and carboplatin were discontinued (Socinski MA and Garnick MB, 1988).

Oxaliplatin: Oxaliplatin is a third-generation platinum-based alkylating agent. A case series published presented six cases of acute pancreatitis presumably related to the use of oxaliplatin. The patients had various gastrointestinal cancers and were receiving oxaliplatin in addition to other chemotherapy drugs. Most of the patients were male (n=4), with a sex ratio of 2:1 and a mean age of 62 years. The latency period was not described in the case series. High levels of pancreatic enzymes were recorded, with an average lipase level of 536 U/L. Investigations including abdominal CT scans and blood tests were performed, ruling out all other plausible causes of acute pancreatitis before considering oxaliplatin as the potential culprit. Upon discontinuation of oxaliplatin, all patients experienced remission of their symptoms and signs, accompanied by a decrease in serum lipase and amylase levels (Nashwan AJ, *et al*., 2015; Bilir C, *et al*., 2012; Nashwan AJ, *et al*., 2016).

The strengths of our review include detailed clinical observations from all collected studies on DIAP induced by platinum salts as a rare complication, contributing valuable data to the limited existing literature. The timely diagnosis and effective management of this condition highlight the importance of vigilance in chemotherapy protocols, offering educational value for clinicians. However, limitations include reliance on case reports, which restrict generalizability, and the absence of long-term follow-up on patient conditions. Some reports were rated low to moderate quality according to the JBI critical appraisal checklists for case reports and case series; they lacked consistent latency patterns and did not adequately discuss challenges and outcomes (Ektov VN, *et al*., 2024; Harland SJ, *et al*., 1985; Singh V, *et al*., 2010)

Furthermore, there was limited information regarding administered doses and latency periods as well as conducted investigations.

The purpose of our review was to describe the link between platinum salts and the development of DIAP in cancer patients. A total of 12 cases have been reported over the last 30 years. Based on current literature, it is highly recommended to include baseline risk assessments for factors associated with acute pancreatitis and to consider acute pancreatitis in the differential diagnosis of abdominal pain in patients who have received platinum-based chemotherapy (Butt W, *et al*., 2010; Bunin N, *et al*., 1985; Tarin F, *et al*., 1994; Zhao C, *et al*., 2024)

CONCLUSION

The review and the case report highlight the rare but serious occurrence of platinum salts-induced acute pancreatitis in patients undergoing treatment for advanced cancers. Physicians must remain vigilant regarding less common adverse effects, such as DIAP, even as platinum salts continue to be widely used in the treatment of various malignancies, including lung cancer. Early identification and intervention are essential to prevent further complications and ensure patient safety.

This case report underscores the importance of personalized adjustments in managing chemotherapy-related toxicities; the prompt replacement of cisplatin with carboplatin allowed for the continuation of chemotherapy without recurrence of pancreatitis. Understanding these side effects is important for improving patient outcomes and maintaining the delicate balance between tolerability and efficacy in cancer treatment, especially as more patients receive regimens based on platinum salts.

ETHICAL COMMITTEE CONSENT

Written consent was obtained from the patient for the use of data in the publication of this case report, and approval was granted by our Institution's Ethics Committee (reference no. 19/24).

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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