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Activity of pemetrexed in recurrent, metastatic sacral chordoma: A case report

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ABSTRACT

Chordomas are a rare slow growing tumor with a high recurrence rate that originate from residual embryonic notochord cells, primarily affecting the axial skeleton. Currently limited treatment options exist beyond surgery and radiation, and systemic chemotherapy has shown limited efficacy. The majority of chordomas exhibit negative thymidylate synthase (TS) expression, implying a potential responsiveness to the antifolate agent pemetrexed. We present a case report of a 78-year-old patient with recurrent, metastatic sacral chordoma who showed clinical and radiological improvement with pemetrexed treatment. The patient received 12 cycles of pemetrexed which resulted in a decrease in the size of liver and lung lesions. Moreover, the patient experienced resolution of debilitating symptoms, including right leg weakness, and unsteady gait. This case report highlights the use of pemetrexed as a therapeutic option for recurrent and metastatic chordoma. Further research is warranted to explore the optimal use of pemetrexed in chordoma management and identify predictive biomarkers for treatment response.

Introduction

Chordoma is a rare and challenging malignant tumor that arises from remnants of the embryonic notochord. It primarily affects the axial skeleton, most commonly occurring in the sacrum, skull base, and vertebral column. Although it rarely metastasizes, it exhibits local invasiveness and destructiveness. Chordomas typically present with mass effect, causing displacement of adjacent structures such as the brainstem, cranial nerves, nasopharynx, and spinal cord. They account for 1 % of intracranial tumors and 4 % of all primary bone tumors (Radaelli et al., 2020; McMaster et al., 2001). Sacrum is the primary site in approximately 30–50 % of cases, while the spheno-occipital region and vertebral bodies are affected in 30–35 % and 15–30 % of cases, respectively (McMaster et al., 2001; D'Amore et al., 2018). Histologically, chordomas are classified into three subtypes: conventional/chondroid, poorly differentiated and dedifferentiated. The typical and chondroid subtypes have a more indolent course, with a 3-year overall survival rate of 90 %, whereas the dedifferentiated subtype is more aggressive.

Chordomas predominantly occur in male Caucasians, with the highest incidence observed at 50–60 years of age (Bakker et al., 2018). Prognosis is generally poor due to the locally aggressive and recurrent nature of the tumors, as well as their resistance to standard radiotherapy and chemotherapy. The 10-year overall survival rate is approximately 40 % (McMaster et al., 2001). Surgical resection followed by adjuvant radiation therapy is the accepted standard of treatment, although complete resection is challenging due to the proximity of chordomas to critical vascular and neural structures (Sanusi et al., 2018; Zileli, 2017). The limited understanding of the underlying drivers of chordoma, characterized by a relatively ``quiet'' genome with few known genetic alterations, has hindered the development of targeted therapies (Tarpey et al., 2017).

The use of pemetrexed, a multitargeted antifolate agent that has demonstrated efficacy in various solid tumors, including non-small cell lung cancer and mesothelioma is under investigation (Adjei, 2004). Pemetrexed exerts its effects by inhibiting key enzymes involved in nucleotide synthesis and folate metabolism, such as thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT), leading to cell cycle arrest and apoptosis (Adjei, 2004; Adjei, 2003). Pemetrexed undergoes intracellular transport, undergoing metabolism to its primary pentaglutamate form, which demonstrates an inhibition of thymidylate synthase (TS) at

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least 60 times more potent than the monoglutamate form Shih et al. (1998). Recent preclinical studies have suggested that pemetrexed, which specifically targets folate metabolism, holds promise as a potential treatment for chordoma. These studies have identified negative TS expression as a potential biomarker that predicts the therapeutic sensitivity of pemetrexed in chordoma, as TS inhibition leads to cell cycle arrest and apoptosis (Kesari et al., 2023a). The recognition of negative TS expression as a potential predictive marker has significant implications for personalized treatment approaches. Validating this biomarker in clinical settings could aid in the selection of patients who are more likely to benefit from pemetrexed-based therapies.

In this case report, we present the clinical management of a patient with recurrent, metastatic sacral chordoma who underwent salvage therapy with pemetrexed with positive partial response and clinical improvement. The CARE checklist has been completed by the authors for this case report (Riley et al., 2017).

Case presentation

A 78-year-old patient with a history of recurrent, metastatic sacral chordoma. Initially completed sacral chordoma resection followed by proton beam therapy (42 sessions). He had three local recurrences within the first 5 years, but then did well for 8 years until developing a fourth local recurrence. At 17 years post-initial diagnosis, he developed an oligometastatic liver lesion and a lung lesion and underwent partial hepatectomy. Soon thereafter, he developed radiological disease progression with increased liver metastases (Fig. 1**)** and extensive new bone lesions throughout the thoracic and lumbar regions however lung lesions were stable over years. He developed right leg weakness and an unsteady gait. Thymidylate synthase (TS) immunohistochemistry was performed through Neogenomics and returned negative, indicating a potential therapeutic benefit of pemetrexed (Kesari et al., 2023a). Due to the patient's negative TS expression, the progressive liver and bony metastases, and the lack of response to previous standard treatments, pemetrexed was chosen as a salvage therapy. Patient initiated pemetrexed 500 mg/m^2 IV every three weeks. Serial imaging was performed approximately every two months to monitor treatment response. After two cycles of treatment at a dose of 500 mg/m^2, measurements of his liver lesions demonstrated a decrease in size and lung lesions were stable. Five months later, pemetrexed dose was increased to 900 mg/m^2 during cycle 6 based on the patient's tolerance and emerging evidence suggesting higher doses could improve efficacy without significantly increasing toxicity in chordoma (Kesari et al., 2023a). Patient noted increased fatigue and nausea for the first 5 days after infusion, otherwise no other significant adverse events were reported. Symptomatically, the patient had improved right leg weakness, and gait and imaging at 9 months showed decrease in liver lesions per RECIST criteria as well reduction in lung lesion (Fig. 1C, F). The bone lesions continued to be stable.

Discussion

Chordoma is a challenging malignancy, and treatment options for recurrent and metastatic cases are limited. Local recurrence rates in chordoma vary from 43 % to 85 %, with a 5-year and 10-year overall survival rate of 70 % and 40 % respectively (Chugh et al., 2007; Ruggieri et al., 2010). As a result, the quality of life for patients is significantly affected. Currently, there are no effective treatments available, and the main options for these patients are repeat resection or radiation, both of which pose a significant risk of morbidity and mortality (Sanusi et al., 2018; Zileli, 2017).

TS has emerged as a key predictive biomarker in the treatment of chordoma, particularly with antifolate therapies like pemetrexed. In a prior study, two cases of metastatic chordoma previously failed multiple medical therapies showed favorable responses to pemetrexed, correlating with negative TS expression (Kesari et al., 2023a). Case 1 was a 56-year-old male with clival chordoma treated with 900 mg/m^2 every 3 weeks for 4 cycles, while Case 2 was a 64-year-old male with stage IV sacral chordoma received 900 mg/m^2 every 3 weeks for 28 cycles (Kesari et al., 2023a). Furthermore, a recent pilot study of IV pemetrexed 900 mg/m^2 every 3 weeks with supportive medications (e.g. folic acid, vitamin B12 and dexamethasone) between February 2020 and June 2021 reported promising results, suggesting that high-dose pemetrexed is well-tolerated and exhibits antitumor activity in

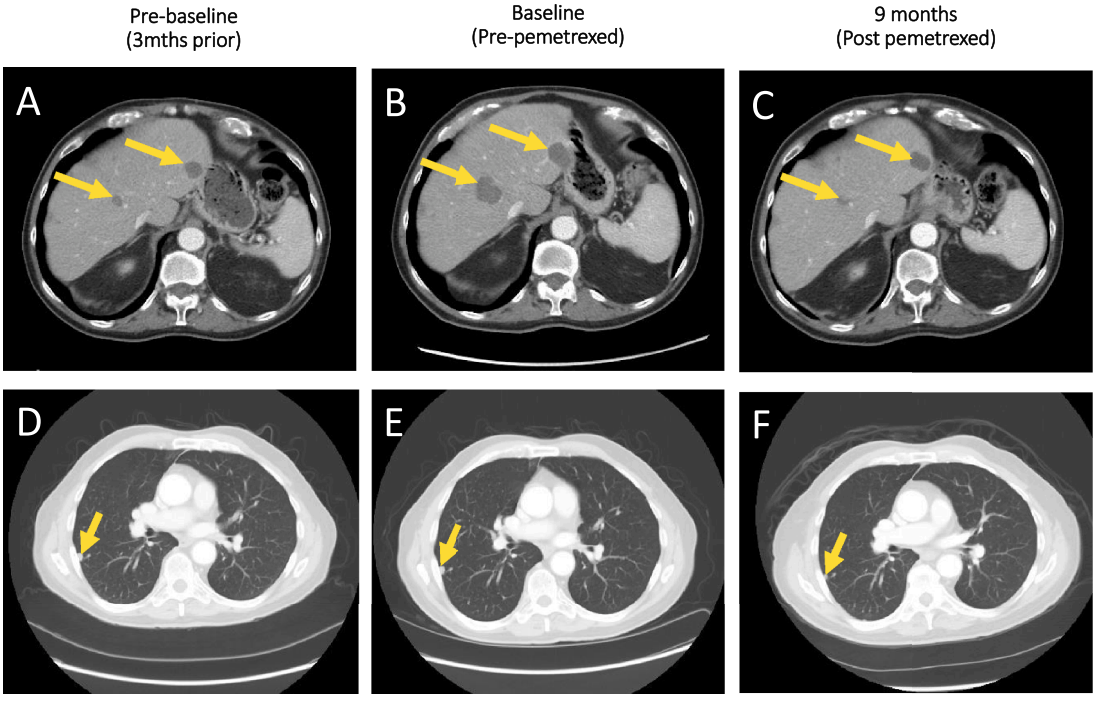

Fig. 1. A–C: Abdominal CT with contrast showing changes in the size of tumors in the liver before and after treatment with pemetrexed. D–F: Chest CT with contrast showing changes in the size of lung tumors before and after treatment with pemetrexed.

patients with progressive chordoma (Kesari et al., 2023b). Results from reported cases involving 14 patients revealed that 2 (14 %) achieved a partial response, while 10 (71 %) showed stable disease (Kesari et al., 2023b). Like our case report, the studied chordoma cases demonstrated tolerability and tumor shrinkage with response to pemetrexed treatment correlating to TS expression.

In this case report, we present the clinical management of a patient with recurrent, metastatic sacral chordoma who underwent salvage therapy with pemetrexed. Given the specificity of our findings to this individual patient, an inherent limitation of this case report is the lack of generalizability to the broader population. Pemetrexed, a multitargeted antifolate agent, has demonstrated effectiveness in various solid tumors, including non-small cell lung cancer and mesothelioma. Recent pre-clinical studies have identified negative TS expression as a potential biomarker for predicting pemetrexed sensitivity in chordoma (Kesari et al., 2023a). Based on our findings and the available medical literature, we conclude that pemetrexed shows promise as a therapeutic option for recurrent and metastatic chordoma. The positive clinical and radiological responses observed in our patient, along with the resolution of debilitating symptoms, support the therapeutic efficacy of pemetrexed in this context.

The rarity of chordomas restricts current evidence to small-scale studies, underscoring the necessity for larger prospective trials to validate these findings and determine the optimal treatment approach. The heterogeneity of chordoma subtypes and the limited number of patients enrolled in studies present challenges in generalizing the results to all chordoma cases. Additional research and controlled clinical trials are necessary to further evaluate the efficacy, safety, optimal dosage, and treatment duration of pemetrexed in chordoma management. Furthermore, validation of negative TS expression as a predictive biomarker in clinical settings would aid in patient selection for pemetrexed-based therapies.

Conclusion

Due to the rarity of chordomas, there has been limited literature addressing novel treatment strategies and a lack of clinical trials available. This case report highlights the potential activity of pemetrexed in the treatment of recurrent and metastatic chordoma, particularly in patients with negative TS expression. Further research is warranted to validate these findings, optimize treatment strategies, and identify additional predictive biomarkers for treatment response. The insights gained from this case report contribute to the growing understanding of chordoma management and emphasize the need for continued exploration of novel treatment approaches, particularly those utilizing biomarkers for targeted therapies.

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Availability of data and materials

All data generated or analyzed during this study are included in this article and its online supplementary material. The data generated in the present study may be requested from the corresponding author.

Ethics approval

Data for this case report was collected under retrospective human subjects protocol JWCI-19-1101 that is approved by the Providence St. Joseph Health Institutional Review Board.

Patient consent statement

The authors declare that they have obtained consent from the patient.

CRediT authorship contribution statement

Dominique G. Celestino: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Lara E. Davis:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Santosh Kesari:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no competing interests.

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