

Hypertrophic pachymeningitis during radiotherapy for locally advanced prostate cancer: A coincidental or causal relationship

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ABSTRACT

Hypertrophic pachymeningitis (HP) is a rare clinical disorder characterized by focal or diffuse thickening of the dura mater with various neurological manifestations. It is known to be associated with autoimmune diseases, infections, and neoplasms. However, a review of the literature did not reveal that HP occurs during radiotherapy for cancer. In this report, we present a rare case of HP during radiotherapy for cancer in a 71-year-old male patient with high-risk prostate cancer who developed a headache and abducens nerve palsy during radiotherapy following androgen deprivation therapy. Magnetic resonance imaging (MRI) revealed dura mater thickening without brain metastases. The cerebrospinal fluid analysis demonstrated elevated protein levels. The patient was diagnosed with HP and treated with oral prednisolone. Within 2 days of treatment, the headache subsided, and the abducens nerve palsy resolved completely after 6 months of radiotherapy. In view of these events, we suggested a possible correlation between radiotherapy and HP, particularly, if meningitis develops during radiotherapy in the absence of infection or cancer seeding.

Key words: Abducens nerve palsy, Adverse effects, Dura mater, Hypertrophic pachymeningitis, Radiation-induced abnormalities

Hypertrophic pachymeningitis (HP) is a rare clinical disorder characterized by focal or diffuse thickening of the dura mater with various neurological manifestations such as headache, cranial nerve palsy, cerebellar ataxia, and paralysis [1,2]. HP is associated with several autoimmune diseases such as antineutrophilic cytoplasmic antibody-associated vasculitis, rheumatoid arthritis, sarcoidosis, and immunoglobulin (Ig) G4-related disorder; infections such as tuberculosis, syphilis, and fungus diseases; neoplasms such as lymphoma, but in some cases, the cause of HP is unknown [1,2]. To our knowledge, there have been no reports of HP during radiotherapy for malignant tumors. Here, we report a rare case of HP that developed during radiotherapy for locally advanced prostate cancer to increase the awareness of clinicians of HP as a possible complication of radiotherapy.

CASE REPORT

A 71-year-old man with no significant past medical history was referred to our institution for radiotherapy for high-risk prostate cancer (initial prostate-specific antigen [PSA] 20.2 ng/mL, Gleason score 4+3, cT2c N0 M0) after 6 months of maximal

androgen deprivation therapy (MADT). Six months after MADT, PSA levels dropped below the detection limit. The patient underwent intensity-modulated radiation therapy (IMRT) at 2 Gy per fraction, for a total dose of 76 Gy. When 14 Gy of IMRT was performed, diplopia and headache appeared. Fundoscopy revealed no abnormality, but right abducens nerve palsy was noted.

Brain magnetic resonance imaging (MRI) showed no brain metastases or brainstem lesions (Fig. 1a), but the dura mater was diffusely thickened. Contrast-enhanced MRI showed enhancement of the dura mater (Fig. 1b). Cerebrospinal fluid (CSF) analysis showed total proteins of 0.875 g/L (normal: 0.15–0.45 g/L), cell count of 2 lymphocytes/uL, and glucose level of 70 mg/dL (normal: 50–80 mg/dL), whereas the CSF microbiology study was negative for Gram stain and no growth of microorganisms was observed. Concentrations of IgG, IgM, and acetylcholine receptor antibodies in CSF were all within normal limits. Blood test results showed an aspartate aminotransferase level of 55 IU/L (normal: 11–35 IU/L), and lactate dehydrogenase levels of 373 IU/L (normal: 105–237 IU/L). Complete blood count tests, kidney function tests, PSA level, C-reactive protein level, and levels of IgG and IgM were within normal limits. Based on MRI findings, CSF analysis, and blood tests, a diagnosis of HP was made, which was most likely attributed to radiation therapy. Oral prednisolone

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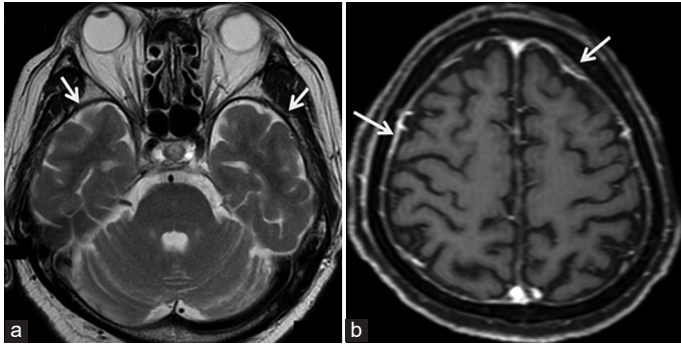


Figure 1: MRI of a 71-year-old man with hypertrophic pachymeningitis. (a) T2-weighted MRI shows no intramedullary lesions. The dura mater is thickened (arrows). (b) Gadolinium-enhanced T1-weighted MRI demonstrates diffuse thickening and enhancement of meninges (arrows). MRI: Magnetic resonance imaging

was administered at a dose of 30 mg/day, which relieved the headache within 2 days, but the abducens nerve palsy remained. Prednisolone was continued during radiotherapy, but the dose was gradually tapered in the next days and finally discontinued after 2 weeks of radiotherapy. MADT was also stopped when radiation therapy was completed. The post-treatment course was uneventful, with no adverse events or relapses occurring during the 6-month follow-up after radiotherapy. Diplopia and abducens palsy gradually improved without treatment and were completely cured 6 months after radiotherapy.

DISCUSSION

HP can be caused by a variety of diseases, including infections (tuberculosis, syphilis, and fungal infections), autoimmune/inflammatory diseases (granulomatosis with polyangiitis, sarcoidosis, and IgG4-related diseases), malignancies, and drug reactions; however, the cause is often idiopathic [1,2]. To our knowledge, this is the first case suggesting that cancer radiation can trigger HP.

HP has a variable clinical presentation depending on the underlying etiology and location of the lesion, as well as the thickness of the dura mater on brain imaging. Headache and multiple cranial neuropathy are the most common clinical manifestations. Extran neurological or systemic manifestations of HP may help define the etiology [3]. Contrast-enhanced MRI imaging is essential for HP diagnosis and its progression monitoring [4]. However, the etiological diagnosis of HP through clinical, laboratory, and imaging workup remains a challenge, and the final diagnosis is usually performed with tissue biopsy. It is essential to rule out infectious diseases, autoimmune/inflammatory diseases, and malignancies, especially lymphomas [3].

We hypothesized that the HP in our patient was most likely due to radiotherapy because there were no extraneurological manifestations, or systemic symptoms suggestive of the underlying etiology; in addition, MRI showed no metastases, whereas CSF studies were negative for infection with normal levels of IgG, IgM, and acetylcholine receptor antibodies. The pathogenesis of

HP during radiotherapy is unclear. We propose that radiotherapy-induced tissue damage and antigen release [5,6], followed by an autoimmune reaction are the possible mechanisms.

Treatment of HP depends on the underlying predisposing factor. For example, if the infections are the cause of HP, treatment would focus on treating the infection [7]. In idiopathic HP, the most commonly used regimen is steroids (prednisone 1 mg/kg/day) [3]. On the other hand, the treatment of radiotherapy-associated HP is unclear. In our case, early initiation of oral prednisolone proved remarkably effective, resulting in complete resolution of headache within 2 days and complete abducens nerve recovery 6 months later. However, strict exclusion of infectious causes is essential for the introduction of immunotherapy, as in cases of idiopathic and autoimmune/inflammatory HP.

There are some limitations to this case report. First, this is a report of a single case and not a large cohort study. Therefore, the relationship between radiation therapy and HP will remain a subject of debate, as the cause-and-effect relationship has not yet been directly investigated. Second, data on pathological and immunohistochemical findings were not available because tissue biopsy was not performed. Since the biopsy of the dura mater is an invasive procedure that is not free from serious complications, and since there was no suspicion of infection or the spread of cancer cells in the meninges based on MRI and CSF examinations, a tissue biopsy would not be necessary.

CONCLUSION

We observed an association between radiotherapy and HP in our case. However, it is still too early to draw a conclusion as we may only be in the early stages of learning about a possible link between radiation therapy and HP. An important challenge in our case is establishing causality because it is unclear whether the relation between radiotherapy and HP is causal or incidental. Could radiotherapy be considered a new etiological risk factor for HP in the future? To confirm or refute this hypothesis, future studies and clinical research are needed to clarify this issue.

CONSENT FOR PUBLICATION

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

AUTHORS' CONTRIBUTIONS

All authors contributed to the completion of this work. The final manuscript was read and approved by all authors.

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