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Case report

Case Report: Primary pituitary non-Hodgkin's lymphoma developed following surgery and radiation of a pituitary macroadenoma

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ABSTRACT

OBJECTIVE: Primary central nervous system (CNS) non-Hodgkin's lymphoma is a rarely encountered clinical entity. Here we present a case of a primary CNS diffuse large B-cell non-Hodgkin's lymphoma developed on a previously operated and irradiated pituitary macroadenoma. DESIGN-RESULTS: A 60-year-old woman presented with muscle weakness and eye lid ptosis. Thirty years ago, she was diagnosed with a non-functioning pituitary macroadenoma requiring repeated incomplete operations and conventional radiotherapy and accompanied by partial anterior pituitary deficiency. On admission, the magnetic resonance imaging (MRI) identified a pituitary sellar mass extending into the suprasellar region, compressing the optic chiasm and invading the left cavernous sinus. Following transsphenoidal surgery, the histological investigation revealed the presence of a diffuse large B-cell non-Hodgkin's lymphoma without other loci from the systemic staging. Following chemotherapy and despite a marked resolution of the neoplastic pituitary mass in the post-chemotherapy MRI scan, the patient's course was complicated with consciousness deterioration attributed to epileptic seizures and she died of a hospital acquired infection. CONCLUSIONS: Clinicians should include primary CNS lymphoma in the differential diagnosis of an isolated invasive sellar mass. The possible association of primary CNS lymphoma development with the history of operated and irradiated pituitary adenoma is herein discussed.

Key terms: Irradiation, Non-Hodgkin's lymphoma, Pituitary lymphoma, Pituitary macroadenoma

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INTRODUCTION

Pituitary adenoma is the most common cause of a sellar mass, accounting for up to 15% of intracranial neoplasms.[1] On the other hand, primary pituitary lymphomas are very rare, comprising rarely 0.1% of the cases undergoing transsphenoidal surgery.[2] The

presentation of primary pituitary lymphomas can be puzzling since they may be mistaken for pituitary adenomas.[3-5] Only the histological examination can confirm the diagnosis and determine the designated treatment strategy.

Here we present an uncommon case of a diffuse large B-cell non-Hodgkin's lymphoma with primary central nervous system (CNS) involvement. The lesion developed on a previously operated and irradiated pituitary macroadenoma. To our knowledge, this is the third case of a primary pituitary lymphoma developing in patients harbouring a pituitary adenoma and the first to have arisen following pituitary radiation.[6,7] We offer a brief overview of the existing literature and suggest potential underlying mechanisms to explain this rare coexistence.

CASE REPORT

A 60-year-old woman presented to our department reporting generalised muscle weakness and episodes of headache of gradually increasing intensity and frequency in the last month, as well as right eye lid ptosis. She is a mother of two healthy children and had a medical history of a non-functioning pituitary adenoma. Thirty years ago, she had presented with amenorrhea and vision impairment, mainly in the right eye, and radiologic evaluation had identified the presence of a macroadenoma with suprasellar extension; however, data on the precise dimensions are lacking. The hormonal work-up revealed modest hyperprolactinemia and she underwent a transsphenoidal adenomectomy; because of incomplete resection of the adenoma, a frontal craniotomy followed. Unfortunately, the adenoma excision was again incomplete and the surgery was complicated by left optic nerve damage and sight loss. The patient developed multiple anterior pituitary deficiencies requiring hydrocortisone supplementation (20mg daily). The histological investigation confirmed the presence of a chromophobe pituitary adenoma, but further details from her medical record are not available. Two years later, and due to acute right visual loss, she underwent a second, once again incomplete craniotomy and decompression of the right optic nerve. Afterwards, treatment with conventional radiotherapy was considered and she received a total dose of 46 Gy resulting in reduction of the tumour size and improvement of the visual fields. With the exception of a pituitary magnetic resonance imaging (MRI) two years before showing no residual adenomatous tissue, the patient's follow-up was not systematic. The remaining medical and family history was unremarkable.

On admission, clinical examination revealed third nerve palsy, while biochemical investigation was normal except for moderate hyponatremia (Na^+ 124mmol/L). Hormonal work-up confirmed multiple anterior pituitary deficiency: decreased free thyroxine [8pmol/L, NR 9-21, (0.62ng/dl)] and triiodothyronine levels [0.90nmol/L, NR 0.89-2.4 (59ng/dl)] with inappropriately normal thyrotropin levels (TSH 1.2mIU/L), suppressed gonadotrophin levels (FSH 2.6IU/L, LH 0.75IU/L), as well as growth hormone and insulin growth factor 1 levels (GH 0.2 μg/L, NR 0.6-6.6, IGF-1 42 U/ml, NR 122-327). Morning cortisol levels [228nmol/L, NR 138-690 (8.26μg/dl)] were normal (she was under hydrocortisone treatment) and prolactin levels were 24.2ng/ml (NR 1.2-29). There was no evidence of diabetes insipidus. Unfortunately, measurement of a-subunit levels was not undertaken in our patient.

Her symptoms and electrolytic abnormalities resolved with the administration of intravenous fluids and supplementation with hydrocortisone and thyroxine. A relapse of the known pituitary macroadenoma was suspected and a pituitary MRI was performed which identified a pituitary macroadenoma 2.5x2.6cm with inhomogeneous enhancement following intravenous gadolinium administration, extending into the suprasellar region, compressing the optic chiasm and invading the left cavernous sinus and the right side of the pons (Figure 1). The patient underwent a sublabial transsphenoidal surgery and histological investigation revealed the presence of neoplastic tissue with intense degenerative alterations replacing the normal cell architecture. Cell immunohistochemistry was positive for the leukocyte common antigen (LCA), whereas the indices for pituitary hormones and epithelial cells were negative. Moreover, cells were positive to L-26 (CD-20) and PanB, whereas indices to CD-5, Cyclin-D1, bcl-6, CD10 were negative. Cell proliferation index Ki-67 was over 30%.

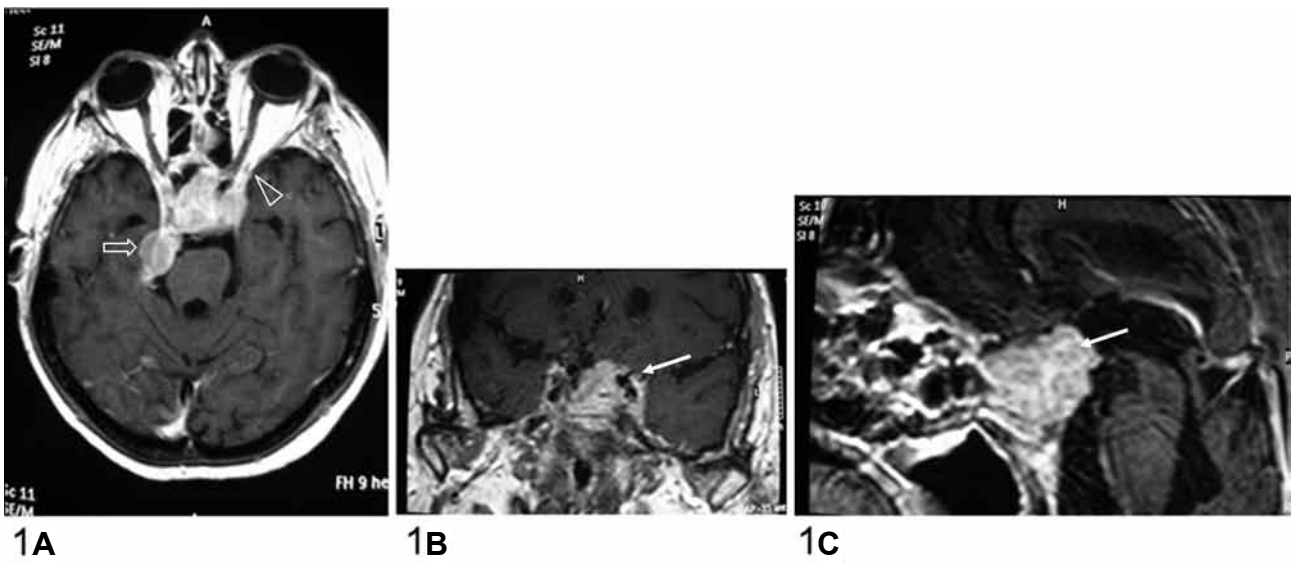

Figure 1. A. Brain MRI scan T1-weighed axial after gadolinium enhancement. **B & C.** Coronal and sagittal T1-weighed pituitary MRI scan respectively. The pre-treatment figures show a sellar mass with diffuse inhomogeneous enhancement after gadolinium administration, which occupy the intrasellar region, suprasellar cistern, extending and surrounding the left cavernous sinus (→), compressing the optic chiasm and reaching the optic canal (▷). The mass produces a slight compression to the pons on the right side in the prepontine cistern (⇨).

The histological results established the diagnosis of a diffuse large B-cell non-Hodgkin's lymphoma (NHL) (Figure 2). Evaluation and staging for systemic disease with thorax, abdomen and pelvis imaging, bone marrow aspiration and CSF analysis excluded other neoplastic foci. Scanning with Ga-67-citrate and testing for the HIV were negative. Systemic chemotherapy with intraspinal methotrexate infusion and the R-MPV chemotherapeutic protocol was administrated, i.e. rituximab 950mg, methotrexate 6.7g, vincristine 2.6mg and procarvazine 1.3g cumulative dose. Seven days later, ophthalmoplegic signs resolved and the post-chemotherapy MRI scan showed a marked regression of the neoplastic pituitary mass with decompression of optic chiasm and left cavernous sinus (Figure 3). The patient's course was complicated with an acute decrease of the consciousness level 20 days after the R-MPV scheme. Her symptoms were attributed to epileptic seizures and after a long hospitalisation period she died of a hospital acquired infection. Unfortunately, no autopsy data were available.

DISCUSSION

We describe an unusual case of a primary pituitary lymphoma that developed many years after surgical and irradiation attempts to treat an invasive pituitary macroadenoma.

On presentation, the clinical findings of our patient orientated us to consider a relapse of the known pituitary adenoma and led to the decision to proceed to a transphenoidal resection of the residual adenomatous tissue. The unexpected histological examination altered the initial clinical working hypothesis and, after exclusion of systemic involvement, the diagnosis of a primary pituitary B-cell lymphoma in an immunocompetent patient was established. The gradual onset of her symptoms and the pituitary imaging were not supportive of a pituitary apoplexy. The hyponatremia was probably related to adrenocorticotropin and TSH deficiency. Although cortisol levels were within normal range under replacement therapy, we feel that the patient did not receive adequate hydrocortisone during this stressful period. Furthermore, according to her medical records she was not under thyroxine replacement despite the thyrotroph dysfunction documented on admission. Another factor that should be mentioned is the inadequate compliance of the patient during therapy and follow-up.

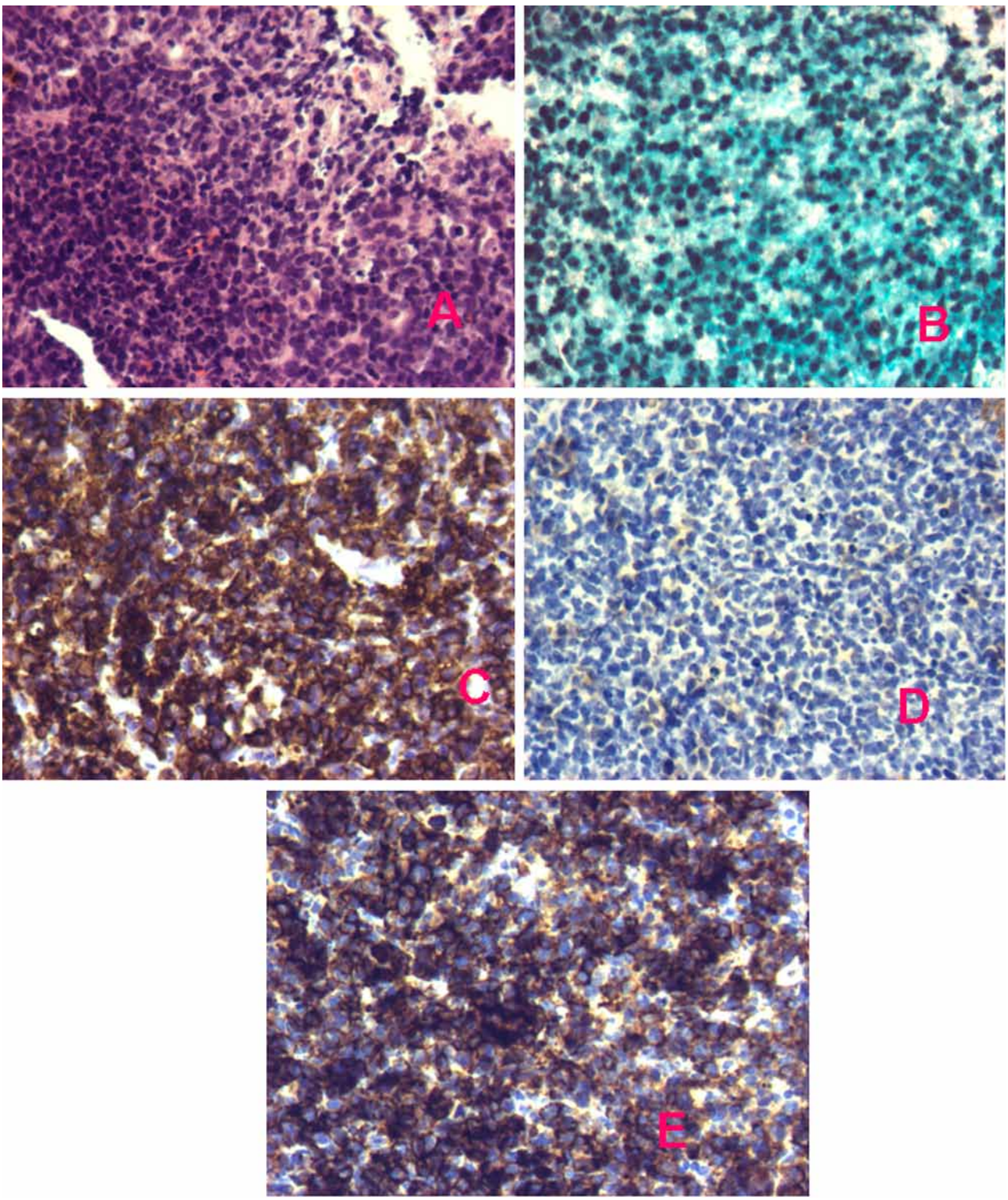

Figure 2. Histochemistry and immunohistochemistry of pituitary neoplastic tissue establishing the diagnosis of a diffuse large B-cell non-Hodgkin's lymphoma (x20). **A.** Hematoxylin-cosine staining. **B.** Ki-67 over 30%. C. L-26 (CD-20). **D.** PanKer. E. PanB.

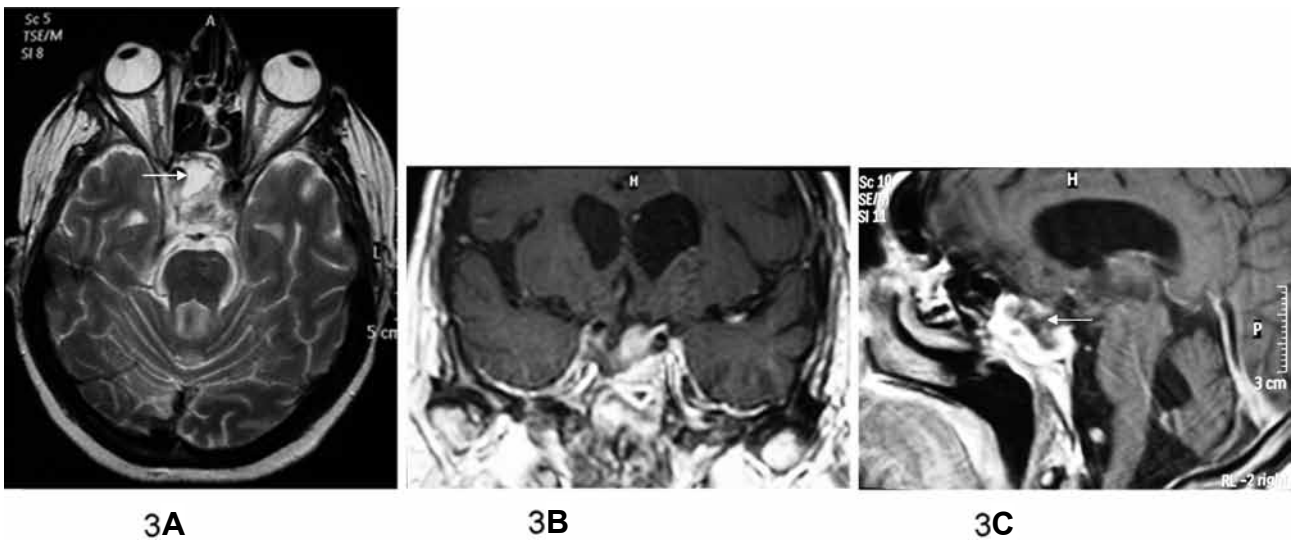

Figure 3. A. Brain T2-weighed axial MRI scan. **B & C.** Pituitary T1-weighed coronal and sagittal MRI scan respectively after gadolinium enhancement, showing a marked regression of the sellar mass with central area of necrosis (post-chemotherapy).

CNS non-Hodgkin's lymphoma is associated with a poor prognosis. It usually arises from metastatic spread of systemic disease, whereas primary CNS lymphoma (PCNSL) is uncommon, constituting 3% of all intracranial neoplasms.[8-10] Even rarer is the sole involvement of the hypothalamus- pituitary region.[11,12] The majority of cases are associated with congenital and acquired immunodeficiency, whereas around 29 case reports with sellar and suprasellar location concern immunocompetent patients, like ours.[4,5,13]

Regarding radiologic evaluation, there are no distinct radiological features of sellar and suprassellar lymphomas that can aid the differential diagnosis. On MRI, they usually appear as iso- or hypointense on T1 and T2-weighted images and tend to have homogeneous enhancement following radio-contrast administration.[14]

To our knowledge, only two previous reports have described the simultaneous existence of a pituitary adenoma with a primary pituitary lymphoma.[6,7] Kuhn et al have reported a patient harbouring a mixed T-cell lymphoblastic lymphoma and a pituitary adenoma with immunoreactivity to FSH, diagnosed 25 years after the initial resection of the adenoma. The second case concerned a patient with a collision tumour, consisting of pituitary adenomatous tissue with immunoreactivity to TSH and chromogranin closely admixed with diffuse large B-cell lymphoma. Our patient had a long history of a recurrent, previously operated and irradiated macroadenoma, but on histology all pituitary markers were negative and the pituitary was replaced by lymphomatous tissue. However, it should be noted that there are null cell adenomas with negative immunostaining for all pituitary hormones. To the best of our knowledge, this is the first report of a primary pituitary lymphoma developing following pituitary radiation for a recurrent macroadenoma.

Brain radiation for pituitary adenomas is a well established risk factor for second brain tumour development.[15] However, the vast majority of these malignancies constitute solid tumours, like astrocytomas, meningiomas and gliomas.[16,17] Primary CNS lymphomas are not particularly common in this setting, even though one could speculate several etiopathogenic pathways.[18]

One cannot exclude the possibility that prior radiotherapy for a pituitary adenoma can exert a carcinogenetic effect on hematopoietic cells, expected to become clinically evident many years following radiation, not only on the site of irradiation but also in other CNS sites; however, lymphomas are radiosensitive and this is contrary to the aforementioned hypothesis. Clearly, the possibility of a preexisting

pituitary lymphoma in our patient is unlikely given the long history of the pituitary adenomas and the known aggressive behaviour and poor outcome of these lesions. In addition, an infectious agent, i.e. Ebstein-Barr or herpes virus, could trigger a chronic lymphocytic inflammation that might transform to a malignant T-cell proliferation, an attractive hypothesis mostly in the setting of immunodeficient subjects,[19] but not easily supported in our immunocompetent patient, who after all was proven to have a diffuse large B-cell lymphoma.

There is literature data supporting the presence of stem cells in the pituitary.[20] These cells, i.e. chromophobes, marginal zone cells, follicular cells, folliculostellate cells and colony-forming units, have the potential to transdifferentiate into different cell types. These multipotent cells might have been activated and proliferated, leading to the development of pituitary lymphoma. Another possible mechanism could be that pituitary irradiation could has induced autoantibody formation and this type of hypophysitis might have led to lymphoma development. This is also supported by evidence showing similar pathogenetic pathways in primary pituitary lymphoma and lymphocytic hypophysitis in immunocompetent patients.[21] This hypothesis parallels the development of primary thyroid lymphoma in patients with Hashimoto thyroiditis. However, the long time period between the initial adenoma diagnosis and the current presentation of the patient make the scenario of radiation-induced hypophysitis as the underlying mechanism of lymphoma development less likely.

Another possible pathway for lymphoma development on adenomatous tissues is the growth stimulating effect of various pituitary hormones. Prolactin, growth hormone, but also gonadotrophins and thyrotropin have been shown to exert mitogenic effects on normal lymphocytes, as well as lymphoma cells.[22-24] Even though there is a possibility of prior trophic action of pituitary hormones, the markers of all pituitary hormones on the present histological examination were negative and the circulating hormonal levels indicated multiple anterior pituitary deficiencies. Finally, the expression of specific adhesion molecules on adenomatous cells acting as a lymphocyte attracting signal could be an alternative pathophysiologic mechanism, although this might better explain a CNS lymphoma with a different primary origin invading the sellar area rather than stemming from it.[25]

In conclusion, we describe a very rare case of primary aggressive CNS lymphoma presenting isolated in the pituitary gland, this being to the best of our knowledge the first case developing many years after radiation therapy of a pituitary macroadenoma. Although one can provide several arguments to interpret the development of non-Hodgkin's lymphoma in a previously operated and irradiated tissue, no definite conclusion can be drawn and most hypothesized pathophysiologic mechanisms remain speculative. Our report emphasizes the need for clinical awareness in such perplexing cases which clearly require a multidisciplinary approach.

Disclosure summary

The authors have nothing to disclose.

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