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Case report

Optic neuropathy following radiotherapy for Cushing's disease: case report and literature review

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ABSTRACT

Radiation-induced optic neuropathy is a rare adverse effect of radiotherapy applied for the treatment of pituitary adenomas. We report a patient with a recurrent adrenocorticotrophin secreting pituitary adenoma who received external beam irradiation after failing surgical and medical therapy. Sixteen months after radiotherapy, the patient was presented with declining visual acuity, and radiation-induced optic neuropathy was diagnosed. Despite treatment with glucocorticoids and hyperbaric oxygen, her vision did not improve. The pathophysiology, prevention and treatment of radiation-induced optic neuropathy, including the efficacy of hyperbaric oxygen therapy are reviewed.

Key words: Hyperbaric oxygen, Optic neuropathy, Pituitary adenoma, Radiotherapy

INTRODUCTION

Cushing's disease (CD) is the most common cause of adrenocorticotrophin (ACTH) dependent Cushing's syndrome, with a prevalence of 39 cases per million.[1] This form of hypercortisolism is most commonly caused by pituitary microadenomas, defined as pituitary tumors less than 10 mm in diameter.[2] Due to their size, pituitary microadenomas are amenable to surgical treatment by transsphenoidal resection, currently accepted as first-line treatment.[3] Despite the lack of consensus regarding the definition of long-term cure following transsphenoidal adenomectomy for CD, reports of long-term remission rates range between 44-79%.[3,4] Hence, a significant number of patients will require additional treatment for CD. Therapeutic options include further transsphenoidal surgery (TSS), bilateral adrenalectomy, medical therapy as well as radiotherapy by means of external beam irradiation or stereotactically-guided irradiation.[3]

Conventional external beam irradiation is an effective and well-tolerated treatment for patients who relapse after TSS for CD, achieving tumor and endocrine control in 80-90% and 50-80% of patients,

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respectively.[3,5-8] Side-effects of this therapy include panhypopituitarism in approximately 50-70% of patients and, rarely, oncogenesis, brain necrosis and radiation-induced optic neuropathy.[6] In this report, we present a patient with severe visual loss following external beam irradiation for late relapse of CD after transsphenoidal adenomectomy. In addition, we review patients' characteristics associated with this devastating complication and describe means of prevention and therapy.

CASE REPORT

A 57-year old woman was diagnosed with Cushing's syndrome, secondary to a pituitary microadenoma in 1990. After transsphenoidal adenomectomy she remained in remission until 2000 when she developed clinical and biochemical relapse of her CD. Magnetic resonance imaging (MRI) of the pituitary gland at the time revealed a recurrent pituitary lesion and the patient underwent a repeat transsphenoidal tumor resection. Postoperatively, her cortisol levels were undetectable (less than 50 nmol/l [1.8μg/dl]) and tumor immunostaining was positive for adrenocorticotrophic hormone (ACTH). Despite apparent initial cure, the patient became cushingoid again. In addition, serum cortisol levels gradually increased, with failure to suppress following dexamethasone administration. Repeat pituitary MRI did not reveal an adenoma and the patient was offered additional treatment including therapy with conventional external beam radiotherapy (RT), which she declined. For two years she was treated with ketoconazole titrated to normal urinary free cortisol levels, occasionally requiring concomitant hydrocortisone administration due to cyclicity of her disease. A trial of cabergoline and long-acting somatostatin analogs failed to control her hypercortisolemia. As no pituitary lesion was shown in pituitary MRI, she finally agreed to undergo pituitary RT. Despite standard recommendations of a radiation dose of approximately 40Gy, she received 54 Gy via 3 ports over 24 sessions, which she tolerated without significant side-effects. However, she remained hypercortisolemic and had to continue adrenolytic treatment until an episode of sepsis occurred following a soft tissue injury, for which she received intravenous antibiotics for four weeks. Following her recovery, her hypercortisolemia was difficult to control on maximum doses of metyrapone and ketoconazole and she therefore underwent bilateral laparoscopic adrenalectomy. Postoperatively, she remained on adequate glucocorticoid replacement and in good health until May 2006, 16 months after completion of radiotherapy, when she reported subacute substantial decline of her visual acuity. Clinical investigation revealed early optic atrophy. Extensive biochemical investigation, autoimmune markers assessment and imaging investigations including lumbar puncture failed to disclose an underlying etiology. Contrast-enhanced MRI revealed evidence of optic neuropathy (Figures 1 and 2). Radiation-induced optic neuropathy (RON) was suspected and the patient received a 5-day course of intravenous glucocorticoids, but her vision continued to deteriorate. Two weeks after the onset of symptoms she received 20 courses of hyperbaric oxygen (HBO) therapy (2 atmospheres for 30 minutes) without significant improvement and currently has only light perception from one eye.

DISCUSSION

Although infrequently used due to its potential for irreversible adverse effects, external beam irradiation remains a relatively safe and effective treatment for CD after failure of surgical management.[6,8,9] Despite its rarity, radiation injury to the optic nerves and

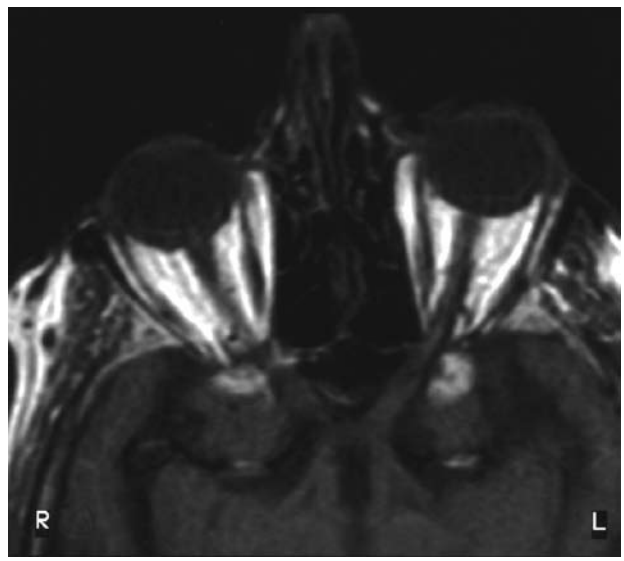

Figure 1. Contrast-enhanced MRI reveals right optic nerve enhancement (T1 spin echo).

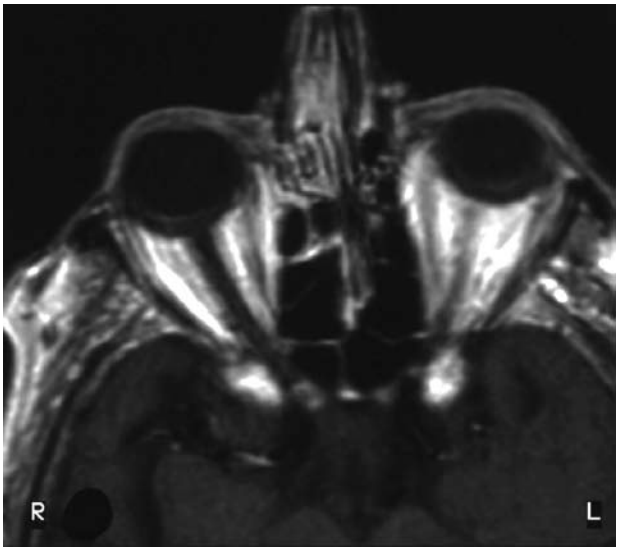

Figure 2. Contrast-enhanced MRI reveals left optic nerve enhancement (T1 weighted spin echo).

chiasm is a known complication of external beam irradiation for pituitary adenomas and presents on average 12 months after treatment, although onset four years after irradiation has been reported.[10] Occurring within weeks after treatment, early pathologic lesions of RON are characterized by inflammation which can be asymptomatic and are generally reversible. In contrast, late lesions occur months to years after treatment completion, are characterized by necrosis and vasculitis and are usually irreversible.[11] Despite previous debate regarding the primary focus of injury, RON is thought to involve both glial and endothelial cells damage leading to an inability of the vasculature to respond to the increased metabolic demands of damaged glial tissue.[12] Stereotactic radiosurgery has achieved more focused delivery of radiation to tumor tissue, reducing the risk for RON and increasing the dose at which RON may occur.[11] However, it requires precise tumor localization. In our patient, no tumor was visible after repeat transsphenoidal tumor resection and therefore she was not a candidate for stereotactic radiosurgery.

When both optic nerves and the optic chiasm are irradiated, approximately 75% of patients develop symptoms affecting both eyes, which are usually sequential.[13] RON manifests clinically with painless visual loss that in many cases progresses to total blindness.[13,14] Diagnosis of RON relies on careful ophthalmologic testing and sequential gadolinium-enhanced MRI to differentiate between RON and recurrent tumor.[10,12,14] However, as RON is a diagnosis of exclusion, a number of autoimmune, inflammatory, infiltrative and occasionally malignant diseases need to be excluded. Our patient's RON presented with typical symptoms and diagnosis was established without delay by use of MR scanning (Figures 1 and 2), ophthalmologic testing and exclusion of other disorders presenting in a similar manner.

The incidence of RON is dose-dependent, increasing with total doses more than 50-55 Gy, single doses more than 10 Gy and/or radiation fraction size greater than 2 Gy.[10,15] For tumors near the optic chiasm, total doses as low as 45 Gy have been reported to cause RON.[16] No cases of radiation-induced optic atrophy were reported in a recent series of 80 patients with CD treated with 45-50 Gy via external beam radiotherapy after failure of surgical management.[8] Similarly, another study using 50 Gy via external beam irradiation found no cases of optic atrophy in 30 patients treated for Cushing's disease.[6] Lower total doses of radiation have been used to treat Cushing's disease with high rates of recurrence and development of Nelson's syndrome.[17] As a relatively high total dose of 54 Gy and daily fractionation exceeding 2 Gy was administered to our patient, this could have contributed to her developing RON.[6]

Additional risk factors for RON include previous radiotherapy to the same field, concomitant administration of chemotherapy, diabetes mellitus and pre-existing visual impairment, all of which were absent in our patient. In as many as 50% of reported cases, no risk factors related to radiation therapy have emerged and no benefit in applying a higher than 45 Gy total radiation treatment dose in all pituitary adenomas has been documented.[18] Some authors have suggested that hypercortisolism in Cushing's patients might make them more susceptible to RON.[10,19] In a large series of patients with clinically non-functioning pituitary tumors (NFPA) treated with radiation, no patient developed RON. A literature review retrieved a total of 11 cases of RON in series reports of radiation-treated NFPA (an overall incidence of 0.53%).[20] Moreover, another series review found that RON occurs in 1.36% of patients with GH-secreting pituitary adenoma treated with radiation therapy, suggesting

that other risk factors, including microvascular damage in association with GH excess and GH secreting pituitary adenoma itself, contribute to higher RON occurrence.[21] At the time when our patient received external beam irradiation, more than two years after recurrence, cortisol levels had been poorly controlled on maximal medical therapy. There are no data about the efficacy of external beam irradiation when administered late in the course of the disease.

Despite reports of spontaneous recovery from RON, this is rare and likely to represent a subset of inflammation-predominant disease.[12,14] Notwithstanding multiple suggested therapies, treatment of radiation-induced optic atrophy remains controversial. Glucocorticoids are still in use even though there is a scarcity of studies demonstrating efficacy and a number of reports showing no benefit.[12,13,22] The use of glucocorticoids in our patient resulted in delaying HBO therapy. Given the lack of data supporting steroid use for RON and some evidence that HBO is more effective if started early after RON onset, steroids should have been avoided. There is evidence that anticoagulants such as heparin and warfarin are effective in cerebral and spinal cord radionecrosis, but no evidence to support their use in RON.[23] A number of reports have shown that RON can occur in patients who were taking these drugs at the time of irradiation.[14,24,25] There is also evidence from an animal model that angiotensin-converting enzyme inhibitors (ACEIs) can reduce the incidence and severity of RON, but these drugs have not yet been used for this purpose in humans.[26]

HBO therapy seems more promising than any other currently available therapy for RON and involves administering 100% oxygen at a pressure between 2-3 atmospheres for 30-60 minutes.[10,12] Oxygen dissolves in the plasma and is delivered to tissues in high concentrations and independent of hemoglobin-bound oxygen. It is thought to reverse radiation-induced ischemic injury by promoting angiogenesis in areas of hypoxia and hypoperfusion.[27] HBO should be started within 48 hours from the onset of visual loss to improve efficacy.[16,28] In the case of our patient, delayed initiation of HBO treatment could have contributed to its lack of effect. Although HBO therapy usually results, in significant improvement, it can very occasionally lead to complete resolution of RON.[16] Since abnormalities in visual-evoked potentials (VEP) and MR signs of radiation-induced injury to the optic pathways can precede symptoms onset, it has been suggested that patients should be followed with serial VEP and MR scans during the period of highest risk after therapy.[29,30] Prophylactic HBO can be administered if such signs are detected in order to maximize its efficacy. However, most patients do not have MR or VEP signs of RON before the onset of symptoms.[12] In addition, the period of highest risk is difficult to define as symptoms can occur up to four years after treatment completion.[10] Although generally regarded as safe, HBO is expensive, time-consuming and may in a few rare cases cause significant side-effects such as optic barotrauma, reversible pulmonary toxicity and seizures, that can occur in up to 0.5% of patients and can be a fatal complication.[12,31] More importantly, only a few reports with a small number of patients support the use of HBO in the treatment of RON,[13,28] while other authors have shown no benefit.[14,16]

In conclusion, RON is a rare but devastating complication of external beam radiotherapy for CD. External beam irradiation remains an effective treatment for patients who relapse after transsphenoidal tumor resection, though currently it is less frequently used due to potential irreversible side-effects. Available data demonstrate that HBO is the most effective of available therapies for RON, although its inconsistent efficacy, potential for side-effects, cost and difficulty in administration render it a less than ideal therapeutic approach. For best results, HBO should be given early after onset of symptoms. The herein described case illustrates the significance of adjusting radiotherapy parameters to prevent RON and underlines factors associated with optimal HBO therapy.

REFERENCES

1. Etxabe J, Vazquez JA, 1994 Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf) 40: 479-484.
2. Mampalam TJ, Tyrrell JB,Wilson CB, 1988 Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. Ann Intern Med 109: 487-493.
3. Bademci G, 2007 Pitfalls in the management of Cushing's disease. J Clin Neurosci 14: 401-408.
4. Atkinson AB, Kennedy A, Wiggam MI, McCance

DR, Sheridan B, 2005 Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. Clin Endocrinol (Oxf) 63: 549-559.
5. Barrande G, Pittino-Lungo M, Coste J, et al, 2000 Hormonal and metabolic effects of radiotherapy in acromegaly: long-term results in 128 patients followed in a single center. J Clin Endocrinol Metab 85: 3779-3785.
6. Estrada J, Boronat M, Mielgo M, et al, 1997 The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. N Engl J Med 336: 172-177.
7. Isobe K, Ohta M, Yasuda' S, et al, 2000 Postoperative radiation therapy for pituitary adenoma. J Neurooncol 48: 135-140.
8. Minniti G, Osti M, Jaffrain-Rea ML, Esposito V, Cantore G, Maurizi ER, 2007 Long-term follow-up results of postoperative radiation therapy for Cushing's disease. J Neurooncol 84: 79-84.
9. Becker G, Kocher M, Kortmann RD, et al, 2002 Radiation therapy in the multimodal treatment approach of pituitary adenoma. Strahlenther Onkol 178: 173-186.
10. Boschetti M, De Lucchi M, Giusti M, et al, 2006 Partial visual recovery from radiation-induced optic neuropathy after hyperbaric oxygen therapy in a patient with Cushing disease. Eur J Endocrinol 154: 813-818.
11. Sheehan JP, Niranjan A, Sheehan JM, et al, 2005 Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium. J Neurosurg 102: 678-691.
12. Levy RL, Miller NR, 2006 Hyperbaric oxygen therapy for radiation-induced optic neuropathy. Ann Acad Med Singapore 35: 151-157.
13. Borruat FX, Schatz NJ, Glaser JS, Matos L, Feuer W, 1996 Radiation optic neuropathy: report of cases, role of hyperbaric oxygen therapy and literature review. Neuroophthalmology 16: 255-266.
14. Miller NR, 2004 Radiation-induced optic neuropathy: still no treatment. Clin Experiment Ophthalmol 32: 233-235.
15. Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR, 1994 Radiation optic neuropathy after megavoltage external-beam irradiation: analysis of time-dose factors. Int J Radiat Oncol Biol Phys 30:755-764.
16. Roden D, Bosley TM, Fowble B, et al, 1990 Delayed radiation injury to the retrobulbar optic nerves and chiasm. Clinical syndrome and treatment with hyperbaric oxygen and corticosteroids. Ophthalmology 97: 346-351.
17. Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Sutton ML, 1990 Long-term follow-up of low-dose external pituitary irradiation for Cushing's disease. Clin Endocrinol (Oxf) 33: 445-455.
18. McCollough WM, Marcus RB, Rhoton AL, Ballinger WE, Million RR, 1991 Long-term follow-up of radiotherapy for pituitary adenoma: the absence of late recurrence after >4500cGy. Int J Radiat Oncol Biol Phys 21:607-614.
19. Brown GC, Shields JA, Sanborn G, Augsburger JJ, Savino PJ, Schatz NJ, 1982 Radiation optic neuropathy. Ophthalmology 89: 1489-1493.
20. van den Bergh AC, Schoorl MA, Dullaart RP, et al, 2004 Lack of radiation optic neuropathy in 72 patients treated for pituitary adenoma. J Neuroophthalmol 24: 200–205.
21. van den Bergh AC, Dullaart RP, Hoving MA, et al, 2003 Radiation optic neuropathy after external beam radiation therapy for acromegaly. Radiother Oncol 68: 95-100.
22. Lessell S, 2004 Friendly fire: neurogenic visual loss from radiation therapy. J Neuroophthalmol 24: 243-250.
23. Glantz MJ, Burger PC, Friedman AH, Radtke RA, Massey EW, Schold SC, Jr, 1994 Treatment of radiation-induced nervous system injury with heparin and warfarin. Neurology 44: 2020-2027.
24. Landau K, Killer HE, 1996 Radiation damage. Neurology 46: 889.
25. Nesh-Meyer HV, Savino PJ, Sergott RC, 2004 Visual loss despite anticoagulation in radiation-induced optic neuropathy. Clin Experiment Ophthalmol 32: 333-335.
26. Kim JH, Brown SL, Kolozsvary A, et al, 2004 Modification of radiation injury by ramipril, inhibitor of angiotensin-converting enzyme, on optic neuropathy in the rat. Radiat Res 161: 137-142.
27. Mayer R, Hamilton-Farrell MR, Van der Kleij AJ, et al, 2005 Hyperbaric oxygen and radiotherapy. Strahlenther Onkol 181: 113-123.
28. Guy J, Schatz NJ, 1986 Hyperbaric oxygen in the treatment of radiation-induced optic neuropathy. Ophthalmology 93: 1083-1088.
29. Kellner U, Bornfeld N, Foerster MH, 1993 Radiation-induced optic neuropathy following brachytherapy of uveal melanomas. Graefes Arch Clin Exp Ophthalmol 231: 267-270.
30. Leber KA, Bergloff J, Pendl G, 1998 Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. J Neurosurg 88: 43-50.
31. Plafki C, Peters P, Almeling M, Welslau W, Busch R, 2000 Complications and side effects of hyperbaric oxygen therapy. Aviat Space Environ Med 71: 119-124.