Regression of a Glucagonoma-Related Paraneoplastic Optic Neuropathy after Surgical Resection

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INTRODUCTION

Pancreatic neuroendocrine tumours (PNETs) account for 5% of pancreatic tumours [1] and are malignant in 50-88% of cases [2]. PNETs can be functioning, i.e., with clinical manifestations due to hormonal hypersecretion, in about 30% of cases. The most frequent functioning PNETs are those related to hypersecretion of insulin and gastrin. Rarely, PNETs may be associated with VIPoma and glucagonoma symptoms [2].

The annual incidence of glucagonomas is about 0.01-0.1 cases/million [2]. This tumour develops at the expense of Langerhans alpha-cell islets, and is commonly unique and large-sized. Its clinical manifestations include necrolytic migratory erythema (NME), weight loss, diabetes mellitus, diarrhoea, anaemia, deep-vein thrombosis, onycholysis, hypolipidemia, hyperprotidemia, and dementia. Ophthalmological manifestations due to glucagonoma have very rarely been described.

The purpose of this report was to describe the case of a patient in whom a glucagonoma was discovered during the workup of a visual loss with bilateral scotoma that regressed after tumour resection, and to provide a comprehensive literature review. Case report A Sixty-five-year-old man presented with bilateral visual loss and central scotoma. The occurrence of diarrhoea and necrolytic migratory erythema were suggestive of a glucagonoma syndrome, which was confirmed by elevated glucagon levels. Computed tomography scan showed a pancreatic tumour, which was a well-differentiated neuroendocrine tumour at pathological examination. Surgical resection was performed and led to the improvement of bilateral visual acuity and complete resolution of scotomas. Discussion The association of paraneoplastic optic neuropathy with pancreatic neuroendocrine tumours have been described 6 and 4 times in the literature, respectively. In larger series, glucagonoma-associated ophthalmological manifestations were reported in up to 14% of cases. Conclusion Glucagonomas may be associated with paraneoplastic optic neuropathy, which can regress after tumour resection.

INTRODUCTION

Glucagonoma-associated ophthalmological manifestations have been exceptionally reported. The purpose was to report the case of a patient with a glucagonoma-related paraneoplastic optic neuropathy that regressed after tumour resection, and provide a comprehensive literature review. Case report A Sixty-five-year-old man presented with bilateral visual loss and central scotoma. The occurrence of diarrhoea and necrolytic migratory erythema were suggestive of a glucagonoma syndrome, which was confirmed by elevated glucagon levels. Computed tomography scan showed a pancreatic tumour, which was a well-differentiated neuroendocrine tumour at pathological examination. Surgical resection was performed and led to the improvement of bilateral visual acuity and complete resolution of scotomas. Discussion The association of paraneoplastic optic neuropathy with pancreatic neuroendocrine tumours have been described 6 and 4 times in the literature, respectively. In larger series, glucagonoma-associated ophthalmological manifestations were reported in up to 14% of cases. Conclusion Glucagonomas may be associated with paraneoplastic optic neuropathy, which can regress after tumour resection.

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Keywords Glucagonoma; Neuroendocrine Tumors; Optic Neuropathy, Ischemic; Paraneoplastic Syndromes

Abbreviations CT computed tomography; PON paraneoplastic optic neuropathy

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zinc, protein and iron levels were normal). The cerebral magnetic-resonance imaging (MRI) was normal. In May 2011, concurrently with ophthalmological symptoms, the patient developed a type-2 diabetes mellitus and diarrhoea. In 18 months, the patient had an 11kg weight loss. Gastroscopy and colonoscopy were performed in October 2012 and were unremarkable. At that time, plasma glucagon level was 204 pmol/L (N: 17-51), chromogranin A 51ng/mL (N: 27-94), gastrin 14.1 pg/mL (N: 13-115), and VIP< 20 (N<60) (Figure 1). An abdominal computed tomography (CT) scan showed a hypervascularized, necrotic and calcified mass, localized in the isthmus and body of the pancreas, measuring 75 mm in diameter. In November 2012, itchy circular erythematous-squamous dermal lesions appeared on the back, with peripheral erythematous border, evoking NME (Figure 3). Glucagon-hypersecreting PNET was then evoked. Pathological examination of endoscopic-ultrasound-guided tumour biopsies showed a grade 2 well-differentiated PNET (proliferative index Ki-67 was 5%). No distant lesion was seen on MRI and chest CT-scan. Somatostatin-receptor scintigraphy showed intense PNET uptake with no evidence of dissemination. Octreotide LP 20 mg every 28 days was then given with symptomatic intent, yielding no significant efficacy on cutaneous lesions, asthenia, diabetes and ophthalmological disease. A pancreaticoduodenectomy (whipple procedure) was performed in February 2013. Pathological analysis showed an 80 mm well-differentiated NET with metastatic lymph-nodes and safe margins, grade 2 (proliferative index Ki67: 5%, mitotic index: 2 per 10 high power fields). Postoperative course was unremarkable. One month after the surgical procedure, the patient had regained 7kg, NME lesions and diarrhoea had resolved, and diabetes was well controlled with low insulin doses. On October 2013, glucagon plasma level normalized at 22pmol/L (Figure 1). Pre-operative ophthalmological
evolution was marked by scotoma persistence, and a progressive worsening of VA (RE 20/200, LE 20/400 in November 2012). After surgery, VA improved rapidly: RE 20/25 in August 2013, 20/20 in October 2013 and 20/20 in March 2014; and LE 20/40 in August 2013, 20/40 in October 2013 and 20/40 in March 2014 (Figure 1). Postoperative ophthalmoscopy showed a decrease of the optic atrophy. Visual evoked potentials showed normal response and visual field examination became normal with scotoma disappearance (Figure 2). One year after the surgical procedure, VA had almost normalized in the right eye and remained stable in the left eye (RE 20/20, LE 20/40) (Figure 1). Regarding PNET, imaging follow-up included a yearly morphological examination by MRI or CT-scan. Eighteen months following surgery, the patient was alive, in good general health, without sign of tumour recurrence and no functioning sign.

DISCUSSION

We described herein an exceptional case of glucagonoma-associated ophthalmological severe manifestations, with dramatic total and sustained relief after curative pancreatic surgery. In the literature, glucagonoma-associated ophthalmological manifestations have been inconsistently reported, with a very low incidence [3, 4, 5, 6, 7]. Nevertheless, glucagonomas are very rare PNETs and it is very hard to determine the precise incidence of their ophthalmological manifestations. The patient’s ophthalmological manifestations (subacute, bilateral, painless and progressive visual acuity loss with paracentral scotomas) were suggestive of optic nerve paraneoplastic syndrome, even more as it has significantly regressed after surgical resection of the pancreatic glucagonoma.

Paraneoplastic optic neuropathy (PON) is often part of complex paraneoplastic syndromes, with cognitive troubles, sensitive neuropathy or myelopathy. PON can also be isolated. PON has been reported to be associated with small cell lung cancer and rarely with B-cell lymphoma, uterine sarcoma, breast, prostate, nasopharyngeal, bronchial, papillary thyroid, non-small cell lung, and renal cell carcinoma [8].

Patients classically present with subacute, bilateral, painless, progressive vision loss. The optic nerve head may appear normal, oedematous, or atrophic. Visual fields may show paracentral scotomas, altitudinal defects and/or peripheral constriction. Bitemporal hemianopsia has also been described in patients in whom PON primarily affected the optic chiasm. T2-weighted MRI examination classically reveals hyper-intense signals in brain parenchyma, or optic nerves or spinal cord abnormalities, or may be normal.

To our knowledge, only 4 cases of glucagonoma-associated visual manifestations have been specifically reported to date (Table 1). The diagnosis of PON could not be confirmed for those cases, but their clinical presentation (i.e., VA loss, optic nerve atrophy and/or scotoma) was highly suggestive of optic neuropathy. The ophthalmological symptoms regressed progressively in all cases, as well as the other clinical symptoms of glucagonomas with the glucagonoma treatment (i.e., surgical removal, chemotherapy or somatostatin analogs) (Table 1).

Hence, these optic neuropathies were very likely to be glucagonoma-associated PON. In a review reporting 21 patients with glucagonoma tumour, 3 of them had visual difficulties (14%) [7], that regressed after treatment of the glucagonoma. Moreover, two cases of non-functioning
PNET have also been reported to be associated with visual manifestations [9, 10]. Ophthalmological symptoms regressed under somatostatin analogs in one case [9], whereas it did not totally resolve after surgery in the other case [10].

Two kinds of serum antibodies can be present in paraneoplastic optic manifestations: anti-CAR IgG in paraneoplastic optic retinopathy and anti-CRMP5 IgG in paraneoplastic optic neuropathy [8, 11, 12]. Collapsin response-mediating proteins (CRMP) are believed to regulate growth guidance cues during neurogenesis. Specifically, the CRMP-5 subtype is found in normal adult retina, optic nerve, and central and peripheral neurons. However, its physiological functions are still unknown [11, 12]. Besides, anti-CRMP5 serum antibodies, also called anti-CV2, are frequently found in the serum of patients affected with paraneoplastic neurological syndromes in general, and the ones affecting the optic nerve in particular [8]. Described as binding to neuronal (but not tumor) cytoplasm [13], and as oligodendrocyte-specific (anti-CV2) [14], each has been reported with paraneoplastic optic neuropathy. In our case, no anti-CRMP-5 antibody was found in the resected post-operative specimen. No patient’s serum was available.

Other aetiologies of optic neuropathy such as vascular pathologies (as arteriosclerosis or inflammatory diseases), nutritional and vitamin deficiencies or toxic causes were searched. The comprehensive evaluation of this case provided no other evidence of other causes. No autoimmune pathology was found. Electroblytes levels were normal (copper, magnesium, selenium, zinc). Vitamin A, E, and C levels were at the lower end of the normal range but not lower enough to explain the symptoms. Vitamin B9, B12, C, D and K1 levels were normal. Protein and albumin levels were normal at the beginning of the case.

In conclusion, this very rare case showed that PON can be associated with glucagonoma syndrome. PON could be an early symptom of the glucagonoma syndrome, as it can appear before NME. Patricians should be aware of the possible association of glucagonoma as with PON and its regression after tumour resection.

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### References


