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Case Report

NUT carcinoma of the sinonasal tract infiltrating the orbit in a man with birdshot chorioretinitis

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Abstract

A 48-year-old man with a history of birdshot chorioretinitis presented with blurry vision, retro-bulbar pain and sinusitis. Though visual acuity was unaffected, he had left optic disc oedema and mild restriction of left eye abduction. His symptoms progressed quickly, with diplopia in primary gaze, epistaxis from his left nostril, and a left relative afferent pupillary defect (RAPD). On computed tomography, there was a mass in the nasal cavity that extended through the left cribriform plate and lamina papyracea and posteriorly into the optic canal.

Pathological examination of biopsy specimens revealed sheets of undifferentiated cells with extensive areas of necrosis and islands of squamous differentiation. The tumour cells expressed monokeratin, p63, CD34, and p16. Molecular testing indicated rearrangement of the *NUTM1* (15q14) locus and fusion of the *NUTM1* and *BRD4* (19p13.12) loci, confirming the diagnosis of NUT carcinoma of the sinonasal tract.

This is the first reported case of NUT carcinoma in a patient with birdshot chorioretinitis. The onset of chorioretinitis may have been the earliest sign of the effects of the BRD4-NUTM1 fusion protein, resulting in expression of HLA-A29. There is evidence that bromodomain and extra terminal (BET) family proteins play a role in inflammatory marker expression.

Keywords: NUT carcinoma, Orbit, Birdshot chorioretinitis, Epigenetics, Bromodomain and Extra Terminal (BET) proteins

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Introduction

Birdshot chorioretinitis is a chronic choroidopathy and vasculopathy that typically occurs in healthy, middle-aged women who are HLA-A29 – positive. NUT carcinoma is a rare, aggressive variant of squamous cell carcinoma characterised by a *NUTM1* (nuclear protein in testis) gene rearrangement. We present the case of a man who developed birdshot chorioretinitis at the age of 38 years and ten years later developed a NUT carcinoma of the sinonasal tract that infiltrated the orbit. A possible genetic linkage between these two uncommon diseases is discussed.

Case report

A 48-year-old man with a 2-month history of sinusitis presented to an optometrist with blurry vision and retro-bulbar pain. On examination, his best corrected visual acuity was 6/6 OU, his intraocular pressures were 18 mm Hg OD and 16 mm Hg OS and his anterior segments were unremarkable.

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He had left optic disc oedema and mild restriction of left eye abduction causing diplopia on left gaze. The patient had a history of birdshot chorioretinitis treated with intravitreal triamcinolone ten years previously and was HLA A29 – positive. His father had glaucoma but there was no other relevant family history. He was immediately referred to an ophthalmologist. On further examination his visual fields by confrontation were full. There was no proptosis and no alteration in colour vision. Fundus examination showed evidence of healed chorioretinitis and left optic disc oedema (Fig. 1). He was sent for an urgent computed tomography (CT) scan of his head.

Two days later, his retrobulbar pain had worsened and he had diplopia in primary gaze. A left relative afferent pupillary defect was accompanied by reduced colour vision on the left side. Hertel exophthalmometry revealed 2.5 mm of left proptosis. He had developed a continuous slow trickle of blood from the left nostril. The CT scan showed a destructive mass in the nasal cavity that extended through the cribriform plate and the lamina papyracea on the left side, pushing on the left medial rectus (Fig. 2). Posteriorly, there was extension into the optic canal. The radiological differential diagnosis included nasopharyngeal carcinoma, sinonasal undifferentiated carcinoma, lymphoma and esthesioneuroblastoma. He was admitted for endoscopic debulking and evaluated by both radiation and medical oncology.

The pathological specimen consisted of numerous fragments of grey-brown, friable tissue. Microscopic examination revealed sheets of undifferentiated cells with nests of squamous epithelium and extensive areas of necrosis (Fig. 3). The sheets were infiltrated by neutrophils and in one small focus the surface epithelium was involved by tumour cells. The tumour cells had oval-round nuclei with vesicular chromatin and small but distinct nucleoli. Mitotic figures were readily recognizable and the cells had a moderate amount of cytoplasm. The tumour cells expressed monokeratin, p63 (strong, nuclear), CD34 (strong, membranous) and p16 (moderate, cytoplasmic, patchy), but there was no expression of S100 protein, HMB45, leukocyte common antigen, chromogranin, or synaptophysin. *In-situ* hybridisation for

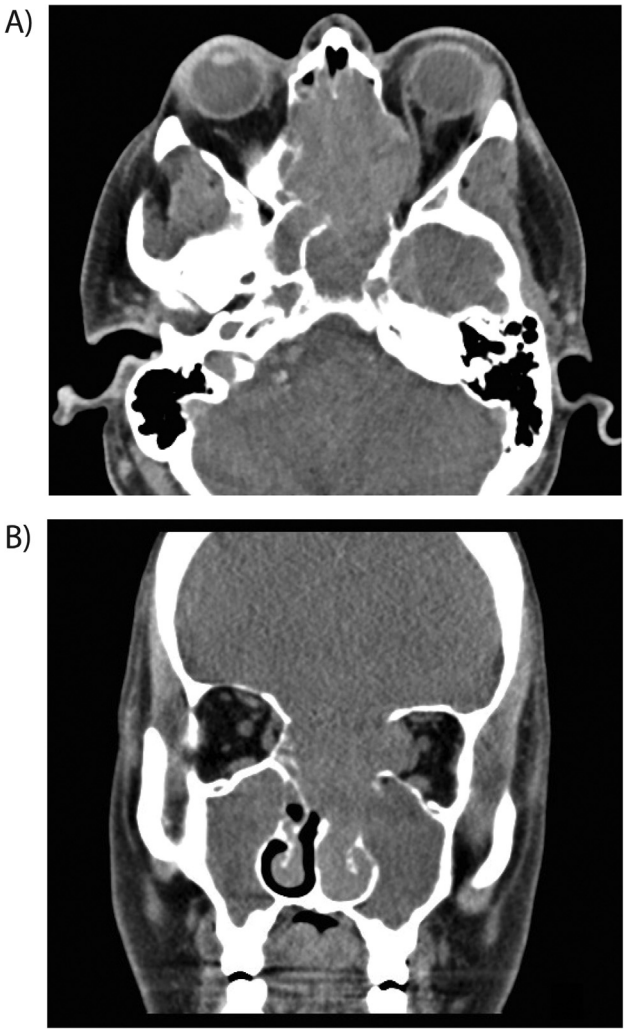

Fig. 2. Computed tomography (CT) scans of the head. The axial (A) scan shows a destructive mass in the nasal cavity extending through the lamina papyracea and abutting the left medial rectus. The coronal (B) scan demonstrates infiltration through the cribriform plate and extension into the optic canal.

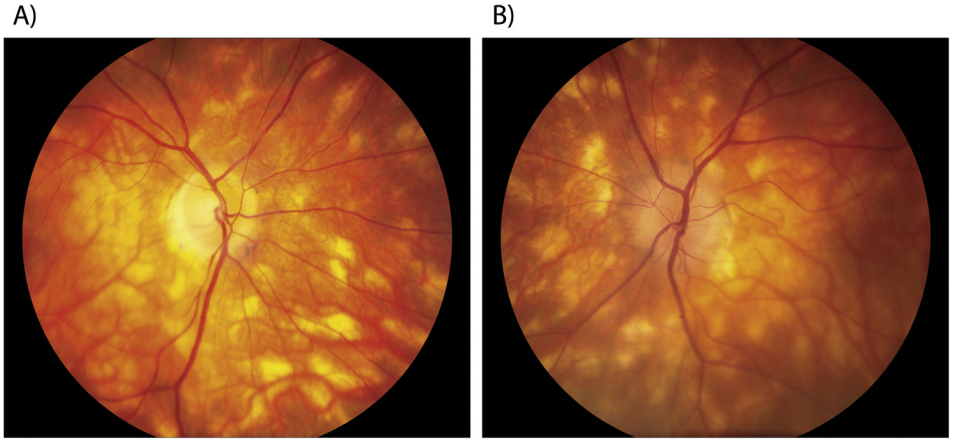

Fig. 1. Colour fundus photographs of the right (A) and left (B) retinas. Both photographs demonstrate the patient's healed birdshot chorioretinitis lesions. The left eye (B) demonstrates optic disc oedema.

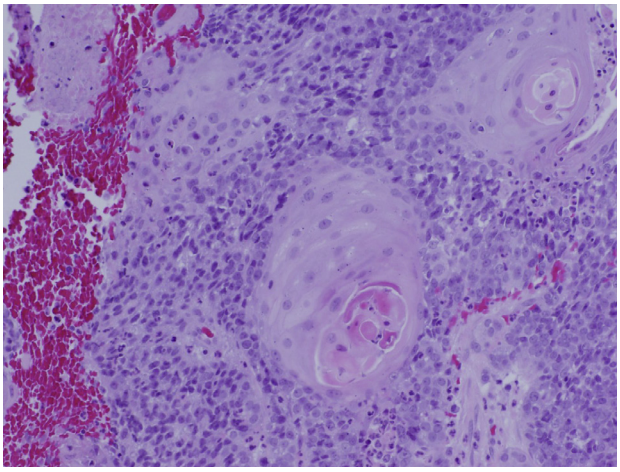

Fig. 3. Tumour biopsy demonstrating undifferentiated cells with a focus of squamous epithelium showing abrupt keratinization. (Haematoxylin & eosin; original magnification 200×).

Epstein-Barr virus was negative. Molecular genetic testing was carried out at the University of Nebraska Medical Center and indicated rearrangement of the *NUTM1* (15q14) locus and fusion of the *NUTM1* and *BRD4* (19p13.12) loci, establishing the diagnosis of NUT carcinoma of the sinonasal tract.

Discussion

The differential diagnosis of small, round blue cell tumours of the sinonasal tract is extensive and includes mucosal melanoma, lymphoma, rhabdomyosarcoma, and a number of unusual carcinomas.[1] NUT carcinoma is a rare and aggressive cancer that typically arises in midline structures,[2] but can also occur elsewhere. It is regarded as a form of squamous cell carcinoma with a predominant undifferentiated component. The carcinoma is characterized by a balanced translocation of chromosomes 15 and 19, resulting in the *BRD4-NUT* oncogene.[3,4] BRD4 is a bromodomain family protein that activates transcription of early G1 genes following mitosis and binds acetylated chromatin through all phases of the cell cycle. Nuclear protein in Testis (NUT) is a mammalian-specific protein expressed in normal spermatocytes and the ciliary ganglion. The function of NUT is unknown, but its structure contains a histone-binding domain. The proposed basis for malignancy in NUT carcinoma is that BRD4-NUT works at the epigenetic level to sequester histone acetyltransferase from genes involved in terminal differentiation, thus preventing their expression.[5]

Approximately one-third of cases arise in the head and neck and two-thirds of these arise in the nasal cavity or paranasal sinuses.[6] The tumour is rapidly-growing and destructive and orbital involvement has been previously described.[7] The tumour occurs at all ages (median age in the 20s) and there may be a slight female predominance. No definite etiological factors have been identified. Metastases may be found at presentation and the tumour carries a grave prognosis with 70–80% of patients dying in the first year. Treatment generally consists of wide local excision followed by chemoradiation but an ideal protocol has not yet been established.[8] Histone deacetylase inhibitors have been tried as adjunctive therapy. The patient described here had some symptomatic relief with radiotherapy, but eventually passed away a few months after presentation from a pulmonary embolus.

Birdshot chorioretinitis is a bilateral posterior uveitis characterised by multiple hypopigmented choroidal lesions clustered around the optic nerve head.[9] It is typically seen in Caucasians in their fourth to sixth decade of life and affects females more than males.[9,10] Birdshot chorioretinitis has a strong genetic association with human leukocyte antigen A29, with up to 95% of patients testing positive for the marker. Approximately 8% of the general Caucasian population are also HLA-A29 positive but never develop birdshot chorioretinopathy. The development of the chorioretinitis is believed to be T-cell mediated, involving interleukin IL-7, but this hypothesis has yet to be fully confirmed.[9] Recent therapeutic trials of IL-7 inhibitors have yielded disappointing results.[9,10]

Our patient with NUT carcinoma would be considered to have an atypical presentation of birdshot chorioretinitis, since he was male and in his fourth decade when diagnosed with the condition. At this time a possible association between these two rare conditions remains speculative. The bromodomain and extra terminal (BET) protein family include BRD2, BRD3, and BRD4 and have recently been implicated in the expression of pro-inflammatory genes.[11,12] Artificial inhibition of BET proteins has been shown to decrease expression of destructive proinflammatory cytokines in *in vitro* models of rheumatoid arthritis[11] and lipopolysaccharide-stimulated macrophages.[12] It is plausible that the first indication of the BRD4-NUTM1 fusion protein affecting our patient was the onset of birdshot chorioretinitis. BRD4-NUTM1 may have triggered expression of HLA-A29 at the epigenetic level, given BRD4's role in regulating the expression of proinflammatory cytokines.

Conclusion

This is the first reported case of NUT carcinoma in a patient with a history of birdshot chorioretinitis. It is possible that the sudden onset of chorioretinitis in this patient 10 years previously may have been the earliest sign of the deleterious effects of the BRD4-NUTM1 fusion protein, resulting in expression of HLA-A29. There is evidence to suggest that bromodomain family proteins play a role in inflammatory marker expression and may be a future therapeutic target in autoimmune inflammatory conditions.[11,12]

Permission to report this case was obtained from the patient's brother.

The case was presented at the annual meeting of the Canadian Ophthalmic Pathology Society held in Montreal, Canada on June 15th 2017.

Conflict of interest

The authors declare that there is no conflict of interest.

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