# Conjunctival myxoma, Zollinger–Ellison syndrome and abnormal thickening of the inter-atrial septum: a case report and review of the literature

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CLINICAL STUDY

**Abstract**

*Purpose* **To report a 36-year-old man with a slowly growing painless bulbar conjunctival mass.**

*Results* **Following excision of the lesion, histological examination was performed and a diagnosis of myxoma was made. A cardiac echogram showed thickening of the inter-atrial septum. Seventeen years previously he had had Zollinger–Ellison syndrome due to gastrinoma of the pancreas which was treated by surgical removal. A review of the literature shows ocular myxomas may be associated with endocrine abnormalities such as Cushing's syndrome, acromegaly, sexual precocity and cardiac myxoma.**

*Conclusion* **In this case we report a novel association of conjunctival myxoma with Zollinger–Ellison syndrome and inter-atrial septal thickening.**

*Key words* Cardiac, Conjunctival myxoma, Endocrine, Zollinger-Ellison syndrome

Myxomas are rare benign neoplasms of mesenchymal origin, with a jelly-like consistency resembling the mucoid tissue of the umbilical cord. Loose connective tissues in bone, genitourinary tract, skin, heart, intestines, nares, sinuses, muscles, joints, pharynx and breast are the known sites of this tumour.[1] These tumours are uni-centric in origin, generally well limited, grow slowly, and spread by mucoid infiltration or expansion but do not metastasise. Recurrences following excision are exceptional.[1] Conjunctival myxoma is extremely rare and the following case report and review is of interest because of its association with an endocrine and cardiac abnormality.

## Case report

A 36-year-old man presented with a history of a slowly enlarging painless nasal bulbar conjunctival swelling, noticed over a period of a few months. There was no abnormal skin pigmentation. Apart from slight discomfort there was no other ocular complaint. Examination of the eye was unremarkable except for a pink gelatinous, cystic, fluctuant, non-tender mass approximately 1 cm × 1 cm in dimension extending into the anterior orbit beneath the conjunctiva (Fig. 1). The mass was freely mobile over the sclera. An attempt to aspirate the fluid failed and did not deflate the lump. The mass was removed through a conjunctival incision; it was gelatinous in texture and was not encapsulated.

An echocardiogram showed an abnormal thickening of the inter-atrial septum, although there was no evidence of myxoma. Early myxoma could not be entirely excluded and it was decided to follow up this patient with regular echocardiograms. During his early twenties he had Zollinger–Ellison syndrome. A gastrin-secreting gastrinoma of the pancreas was removed surgically and confirmed on histology. Screening of first-degree relatives was normal.

### *Pathological examination*

The biopsy showed a well-circumscribed hypocellular lesion composed of stellate and spindle-shaped cells scattered in a myxoid matrix (Fig. 2). Capillaries were scattered throughout the lesion. Mitotic figures were not seen and there was no evidence of necrosis. The lesion did not possess a true capsule, but there was a tendency to condensation of collagen at the edge. No inflammatory response was seen and there was no evidence of any other tissue component such as nerve sheath or cartilage.

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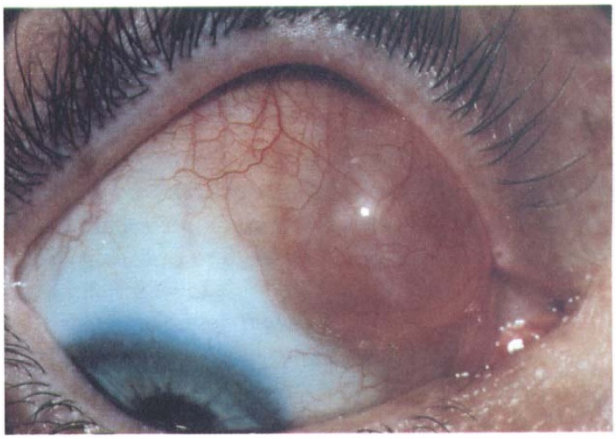

**Fig. 1.** *Anterior segment photograph showing the conjunctival myxoma extending to the anterior orbit.*

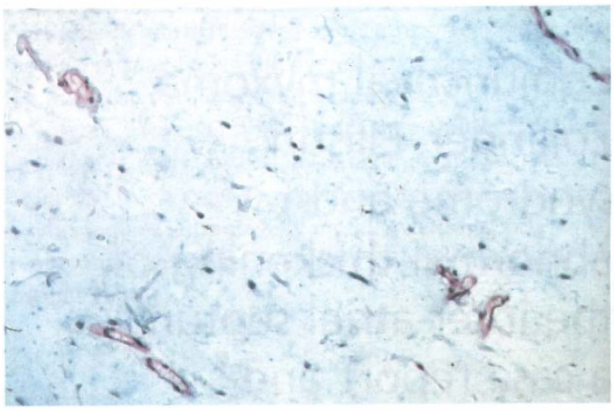

**Fig. 3.** *The myxoid stroma of the tumour demonstrates a positive staining reaction with alcian blue (alcian blue, ×300).*

The myxoid matrix stained with alcian blue (Fig. 3) and this staining reaction was abolished by hyaluronidase.

Immunohistochemistry demonstrated expression of vimentin and CD34 by the tumour cells. There was no expression of S100, desmin, myoglobin, GFAP, cytokeratin or factor VII related antigen. A diagnosis of myxoma was made.

## Discussion

We report a case of conjunctival myxoma associated with Zollinger–Ellison syndrome and thickening of the inter-atrial septum. As far as we are aware, this is a novel association.

Myxoma may involve the conjunctiva, orbit, cornea and lid.[2–11] Conjunctival myxomas are rare and may present as a painless, freely mobile, slowly growing cystic mass that may extend to the orbit. Aspiration of the contents is not possible. Although benign, conjunctival myxoma may clinically simulate lymphangioma, amelanotic naevus, lymphoma, reactive lymphoid hyperplasia and lipoma.

The majority of reported bulbar conjunctival myxomas occurred on the temporal side and have less frequently affected the nasal side or the inferior and superior bulbar conjunctiva.[3,4,12,13] These well-circumscribed lesions arise from the substantia propria and are covered by conjunctival epithelium.[3,4,13,14] Very often conjunctival myxomas are initially diagnosed clinically as cysts. They are pink in colour and can be fleshy in appearance.[3,4,12–14] The cut surface is viscid and gelatinous in nature. The dimensions may vary from 4 to 16 mm. There is no sex preponderance and the median age is 50 years, ranging from 20 to 77 years.

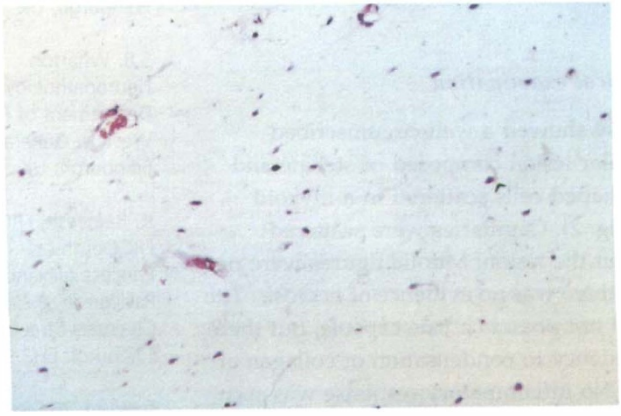

**Fig. 2.** *High-power view demonstrating spindle cells (arrow) in a myxoid matrix (H&E; ×300).*

Histologically, myxomas consist of scattered stellate cells disposed in a mucinous proteoglycan matrix with a network of reticulin fibres.[1,12–15] The stroma stains with alcian blue and on pre-treatment with hyaluronidase becomes alcian blue negative, confirming its hyaluronic acid content. The presence of mast cells is an additional histological feature in conjunctival myxomas. Ultrastructurally the spindle-shaped cells show elongated cytoplasmic processes and are enmeshed in amorphous extracellular material containing sparse collagen fibres.[1,7,14]

Immunocytochemical studies on our case demonstrated expression of vimentin, a non-specific mesenchymal marker, and CD34. CD34 is a transmembrane glycoprotein which has been used as an endothelial marker, but which may, in fact, be expressed by a much broader range of soft tissue tumours.[2] The tumour cells in our case did not express factor VIII-related antigen. In contrast, expression of factor VIII-related antigen has been described in cardiac myxomas,[16] although this is controversial; other authors suggest that surface cells may stain but that the tumour cells themselves do not express this antigen.[17]

Microscopically the differential diagnosis of myxoma includes tumours with a myxoid component including myxolipoma, myxochondroma and myxoid neurofibroma.[1] In these entities tumours cells actively elaborate mucin rather than it being a degenerative phenomenon, and the term 'myxoid degeneration' is rather inappropriate.[1] More importantly the true myxoma may be mistaken for richly myxoid malignant tumours such as myxoid liposarcoma, rhabdomyosarcoma, myxoid malignant fibrosarcoma and myxoid chondrosarcoma.[2] Careful search for the specific cellular elements and rich vascularity of malignant tumours will be helpful in the differential diagnosis.[1]

**Table 1.** *The Carney complex*

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|---|
| 1. Myxomas |
| Cutaneous |
| Eye lid, conjunctiva, orbit, external ear, nipples |
| Cardiac |
| Atrium, ventricle |
| 2. Spotty pigmentation |
| Face, eye lids |
| Pigmentation of caruncle and conjunctiva |
| 3. Endocrine overactivity |
| Cushing's syndrome, acromegaly, sexual precocity |
| 4. Schwannomas |

Eighteen cases of conjunctival myxomas have been reported in the literature.[3,4,12–15,18–21] Although Magalif first reported myxoma occurring in the conjunctiva his report lacked histological description. Doughman and Wenk[13] reported the first conjunctival myxoma with histological examination in a 49-year-old woman. The case reported by Maucione[18] consisted of many capillaries and it is not clear whether it was a true myxoma or myxomatous degeneration of granulation tissue. Ffooks[19] reported a case of a myxomatous lesion appearing in proximity to a corneo-scleral trephine procedure and concluded that possibly the lesion was a pseudo-myxoma due to myxomatous degeneration of the filtration bleb.

This relatively benign ophthalmic manifestation may give a clue to an underlying systemic life-threatening condition. Kennedy *et al.*[20] first reported the association of ocular and cardiac myxoma. More recently a heritable syndrome of complex myxomas, spotty pigmentation of the face, lids and caruncle, endocrine overactivity and schwannomas has been recognised and is known as the Carney complex (Table 1).[8,20,22] The cardiac myxomas in this syndrome tend to occur early in life compared with isolated cardiac myxomas.[8,20,22] The endocrine overactivity includes Cushing's syndrome, acromegaly and sexual precocity. The schwannomas of this complex affect the upper gastrointestinal tract and the sympathetic chain.[22]

Not all patients develop all the features of the above complex. Superficial myxomas involving the lids and conjunctiva occur in nearly 37% of the cases.[20] Carney recommended two or more of the following conditions occurring in a characterised fashion for diagnosis: myxoma – cardiac, cutaneous, mammary; spotty skin pigmentation; Cushing' syndrome; acromegaly or gigantism; sexual precocity; or psammomatous melanotic schwannoma.[20]

The patient we report had Zollinger–Ellison syndrome, due to gastrinoma of the pancreas and histologically proven conjunctival myxoma. Although there was no frank evidence of cardiac myxoma, the inter-atrial septal thickening was unusual and early myxoma could not be ruled out. It is possible that this may represent early myxoma and the patient is under regular review. The patient we report did not fulfil the current criteria of Kennedy *et al.*[20] and Zollinger–Ellison syndrome is not a known endocrine anomaly of the Carney complex. However, based on the lineage of neural crest cell development, an interesting pattern emerges. Myxomas are of mesenchymal origin and the major proportion of ocular and peri-ocular mesenchymal tissues are derived from neural crest.[23] Gastrinomas arise from APUD cells in the gastrointestinal system, which also originate from neural crest cells.[24] Schwannomas are benign neoplasms of Schwann cells and involve the upper gastrointestinal tract and the sympathetic chain when they occur as part of Carney complex.[22] The generation of Schwann cells has been clarified recently as being from neural crest cells.[25] Developmentally the cellular origins of myxoma, schwannoma and gastrinoma can be traced to a final common neural crest origin.[23–25] We propose the criteria of the Carney complex may have to be modified to include endocrinopathies of the diffuse endocrine system such as Zollinger–Ellison syndrome.

In the Carney complex the ophthalmic manifestations precede embolic incidents originating from cardiac myxomas and Carney[22] found more than 50% of the patients with this complex suffered a significant embolic event. Recognition of ocular signs may initiate timely screening which may avert catastrophic acute vascular events such as central retinal artery occlusion and embolic stoke.[20] The factors that should increase suspicion are presence of a deeply pigmented lesion (not induced by sun exposure) on the caruncle, conjunctival semilunar folds associated with conjunctival and lid myxomas.[7,8,20] Further this complex is inherited as an autosomal dominant trait and screening of the first-degree relatives may be useful.[22,26]

Whilst infrequent, myxomas should be included in the differential diagnosis of slowly growing painless peri-ocular masses; the diagnosis should be confirmed histologically. A cardiac, endocrine and family screening would be appropriate to reduce the risk of morbidity and mortality.

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