

Atrial myxoma: a tumour in search of its origins

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Abstract

Objective—To determine whether atrial myxomas express antigens suggesting a neural origin.

Design—A retrospective analysis based on immunohistochemical examination of myxoma tissue.

Setting—Atrial myxomas excised by two tertiary referral cardiothoracic surgical units.

Subjects—24 excised atrial myxomas. Three were from known cases of familial myxoma syndrome.

Methods—Immunohistochemical identifications of three neuroendocrine markers (protein gene product (PGP) 9.5, neurone specific enolase (NSE), synaptophysin) and S100 antigen; CD34 and von Willebrand factor; and α smooth muscle actin to identify possible Schwann cell differentiation, endothelial cells, and smooth muscle cells respectively.

Results—The myxoma cells were PGP 9.5 positive in 18, S100 positive in 16, and NSE positive in 12. Of the 12 NSE positive myxomas seven were synaptophysin positive. All tumours that were NSE positive were also S100 and PGP 9.5 positive. The tumour surface was partially covered by myxoma cells, partly by endothelial cells.

Conclusion—The histological appearances of myxomas with stellate cells embedded within a loose connective tissue stroma, abundant basophil cell infiltration, and the presence of pericellular type IV collagen are similar to nerve sheath tumours (neurofibromas) at other sites. A significant proportion of myxomas also express Schwann cell and neuroendocrine differentiation markers. These features cannot prove the origin of myxomas because tumours may develop aberrant phenotype expression but they do accord with the view that myxomas originate from endocardial sensory nerve tissue.

Atrial myxomas arouse considerable clinical interest, their protean presenting features being described in numerous case reports. The chromosomal characteristics of atrial myxomas suggest that they are neoplasms rather than simply organised thrombi¹ but their exact origin is controversial.

The morphological features of myxomas are highly characteristic but not immediately

reminiscent of tumours in other tissues or organs. Myxomas project into the atrial cavity and have a stalk or base incorporated into the endocardium. The lesion can be peeled away from the underlying myocardium from which there is no obvious evidence of an origin. The tumour consists of a myxoid stroma in which are embedded single stellate cells in addition to larger clumps of similar cells often arranged as a collar around open spaces. Types I and III collagen are present in small amounts only but there is a diffuse reticular stroma with fine collagen fibrils on which iron encrustation often occurs. Type IV collagen is present around clumps of myxoma cells. The stroma is very rich in connective tissue mucins and contains large numbers of plasma and mast cells. The stromal stellate cells are regarded as the essential neoplastic element; one view is that they originate in an undifferentiated endocardial connective tissue cell. Nests of such cells around the rim of the fossa ovalis² would explain the predilection of myxomas for this site. This view takes little account either of the histological structure of the tumour or of some interesting clinical correlations. One of us (DK) spotted one report of a myxoma that produced vasointestinal peptide,³ and another that familial atrial myxomas were associated with lentiginosis, cutaneous neurofibromas, blue naevi and pheochromocytomas as well as endocrine tumours in the pituitary and testes.⁴ These associations prompted DK to question whether atrial myxomas have a potential to produce tumours with neuroendocrine differentiation also whether they have affinity with neurofibromas.

Immunohistochemical techniques can be used to identify specific antigens expressed on tumour cells within the tissue and to define phenotypic expression. We have used markers for neural and neuroendocrine differentiation to study a series of myxomas.

Materials and methods

Twenty four atrial myxomas were studied; three of these were known to be familial. The following primary antibodies were used on paraffin embedded sections after tissue fixation in formol saline: protein gene product 9.5 (Ultraclone), neurone specific enolase (ICN Biomedicals), S100 (Dakopaths), synaptophysin 38 (Boehringer), von Willebrand factor (Dakopaths), CD34 (Q BEND/10 Serotec), and α smooth muscle actin (Sigma).

Where single antibody staining was used

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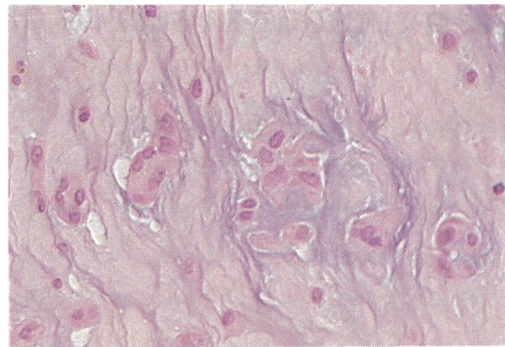
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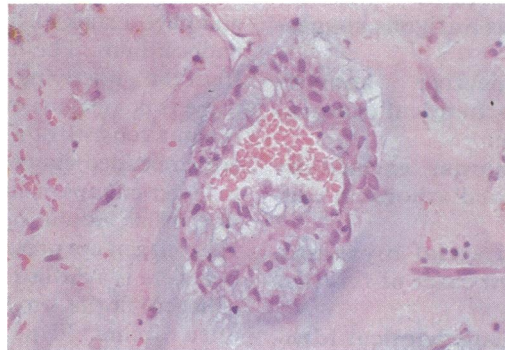
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Figure 1 Haematoxylin and eosin stained sections of atrial myxoma. (A) Small clumps and single myxoma cells embedded in an amorphous stroma that is partly stained blue (basophilia) and partly pink (eosinophilia). (B) A vascular space containing red cells surrounded by a mantle of myxoma cells.



A

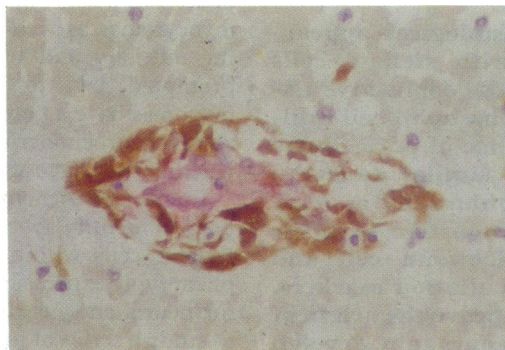


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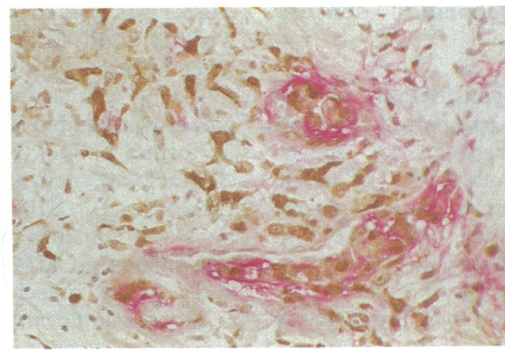
the alkaline phosphatase and monoclonal antialkaline phosphatase (APAAP) technique⁵ was used to identify specific binding. In double antibody studies the first antigen was visualised by the immunoperoxidase ABC method and the second antibody by the APAAP method. Positive (known positive tissues—that is, islet cell tumours) and negative (omission of primary antibody) controls were included in each staining run.

PGP 9.5 (molecular weight 27 000) is a soluble protein extracted originally from brain

Figure 2 Endothelial cells stained red are positive for von Willebrand factor. (A) The surrounding mantle of myxoma cells are stained deep brown indicating the presence of PGP 9.5. (B) Many isolated myxoma cells within the stroma are positive (brown) for neurone specific enolase. There is also some clustering of positive myxoma cells around endothelial cells (stained red) although no vascular lumen is apparent.



A



B

tissue⁶ and present in neurones, nerve axons, and neuroendocrine cell types in normal tissues. Neurone specific enolase^{7,8} is a separate cytoplasmic soluble protein found in axons. S100 protein is found in both Schwann cells and melanocytes in normal human tissue.⁹ Synaptophysin is a glycoprotein isolated from presynaptic vesicles of bovine neurones and is found in all neurones, the adrenal medulla, and in various neuroendocrine tumours including islet cell adenomas.^{10,11} von Willebrand factor/VIII complex and CD34 are present only on endothelial cells. α Actin is found within all smooth muscle cells.^{12,13}

Results

All 24 myxomas showed the typical histological features of clumps and cords of stellate cells with eosinophilic cytoplasm embedded in an abundant myxoid stroma (fig 1A). These cells designated as lepidic (like a butterfly wing scale—one of the more fanciful of pathologists' analogies) also occurred in larger masses arranged as a loose mantle around a space (fig 1B). Immunohistochemical techniques allow recognition of the spatial organisation of the different cell types in myxomas. Endothelial cells identified as containing both CD34 and von Willebrand factor were confined to the centres of clumps of cells and often but not inevitably surrounded a space (fig 2A). The external surface of the myxomas was only partially covered by endothelial cells. Cells staining with PGP 9.5, NSE, S100, and synaptophysin were not present in all myxomas, but when present were confined to the outermost cells of the mantle areas and the isolated stromal cells (fig 2A and B). Eighteen of the 24 myxomas were PGP 9.5 positive, 16 were S100 positive, and 12 were NSE positive. All the myxomas which were NSE positive were also S100 and PGP 9.5 positive. Seven of the 12 NSE positive tumours were synaptophysin positive. In cases with PGP 9.5 positive cells parts of the surface of the myxoma were covered by PGP 9.5 positive cells rather than endothelial cells. Three of the atrial myxomas were derived from patients known to have the familial myxoma syndrome: the stromal cells in one were strongly positive for PGP 9.5 and NSE whereas in the other two they were negative. Smooth muscle cells containing α actin were found predominantly in the base of myxomas where thick walled blood vessels entered from the endocardium. Solid masses of proliferating smooth muscle not obviously related to blood vessels were also present. All of the myxomas showed large numbers of mast cells and plasma cells within the stroma. Macrophages containing haemosiderin were also present in large numbers, reflecting the frequency of haemorrhage from thin walled vessels within the tumour. The stroma showed a biphasic staining pattern with routine haematoxylin and eosin histology stains. There was marked basophilia of the stroma adjacent to clumps of cells while the deeper areas were eosinophilic. The latter areas contained large amounts of insuded fibrinogen, fibronectin, complement, and globulins of plasma origin bound to the connective tissue mucins.

Discussion

The identification of tumour origins by specific antigen expression has to be approached with caution.¹⁴ The phenotypic expression in tumours is variable and does not necessarily reflect their origin. Endocrine functions and expression of neuroendocrine markers that seem inappropriate and independent of the morphological phenotype of the tumour are widely reported in the bowel, ovary, and liver.¹⁵ Nevertheless tumours in which these very aberrant expressions are found are usually malignant whereas myxomas are not. There is also no perfect marker of neuroendocrine differentiation and following the development and use of any particular antibody, its limitations often becomes apparent. For example the gamma subunit of NSE is often expressed in tumours clearly not of neural origin.¹⁶ PGP 9.5 is present in a small proportion of atrial myocytes, in the renal tubule,¹⁷ and in some smooth muscle cells. S100 is also found in adipose cells. Nevertheless, the concordance of positive marking of myxoma stromal cells with three widely used different neuroendocrine markers is presumptive evidence of a neuroendocrine differentiation pattern. Expression of tumour antigens is always capricious and the fact that some myxomas are totally negative does not necessarily contradict the conclusion.

Neurofibromas of other tissues such as the skin and subcutaneous soft tissue are histologically very complex, containing Schwann cells, perineural cells, fibroblasts, endothelial cells, and occasional axons together with large amounts of connective tissue rich in mucins and containing pericellular type IV collagen.¹⁸ Mast cell infiltration is a regular feature and release of vasoactive amines may contribute to an increase in vascular permeability flooding the stroma with plasma derived proteins. Mast cells are also a source of growth factors acting on the Schwann cell element.¹⁹ All of these morphological features including a plasma rich myxoid stroma, a heterogeneous cell population, and mast cell infiltration are found in atrial myxomas. Morphological similarity between two tumour types cannot prove a similar origin but again is evidence consistent with myxomas being neuroectodermal in origin. The atrial endocardium contains many sensory nerves that are a potential origin for nerve tumours.

Given the rather heterogeneous cell population within atrial myxomas it is hardly surprising that previous studies of histogenesis by electron microscopy have been inconclusive. Two studies suggested that several types of mature mesenchymal cell were present^{20,21} while another study regarded the cells as all being of a common undifferentiated mesenchymal form.²²

Previous immunohistochemical studies did not take sufficient account of the microanatomy of the tumour. A briefly held view (when factor VIII/VWF antigen was shown²³) that myxomas were of endothelial origin was discounted when it was realised that only cells in the centre of clumps were positive and the myxoma cells were negative.^{24,25} Smooth muscle cells are also confined to areas with obvious vascular structures.²⁶

The present study suggests that the myxoma surface is partly covered by myxoma cells and

partly by endothelium. This observation confirms a previous study of the surface of atrial myxomas by scanning microscopy.²⁷

If indeed atrial myxomas are of neural origin the finding makes little difference to clinical practice but may explain some of the rarer associations with other manifestations such as cutaneous lentiginosis. Systemic manifestations of myxomas such as fever, hypergammaglobulinaemia, and weight loss may be related to cytokines released from macrophages or mast cells within the myxoma stroma or release of peptides from the myxoma cells themselves.

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