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Review Article

The APUD Tumours- Apudomas

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Abstract

The APUD tumours, also known as Apudomas, refer to the endocrine tumours arising from APUD cells, a group of endocrine cells of the gastrointestinal tract. Apudomas, pathologically, are neoplastic endocrine lesions which take the form of adenoma, adenomatous hyperplasia or carcinoma. Surgery is the only potentially curative therapy

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Introduction

The APUD tumours, also known as Apudomas, refer to the endocrine tumours arising from APUD cells, a group of endocrine cells of the gastrointestinal tract. Hailing its origin from the APUD concept proposed by AG Pearse in early 1960s, Apudomas have been an enigma among the family of endocrine tumours of the gastrointestinal tract - their pathological characteristics unique and their classification mostly depending on the secretory products.

APUD cells are characterized by their high content of amines; their ability of amine precursor uptake, including 5-hydroxytryptophan (5-HTP) and dihydroxyphenylalanine (DOPA); and for their high content of decarboxylase, which helps in converting the precursors to amines. The hypothesis that APUD cells originate from neural crest cells has long been disproven, and recent studies have focussed on the functional manifestations, histological idiosyncrasies as well as the anatomical origins of Apudomas.

Pathophysiology

The APUD cells resemble all polypeptide-secreting cells in their microscopic structure - 100 to 200 μm in diameter and many contain dense storage granules of their polypeptide products. Many of those in the intestine possess long apical processes, which reach the glandular lumen, ending in tufts of microvillus, which may even be sensory. Composed of monotonous sheets of small round cells with uniform nuclei, mitoses are uncommon in Apudomas.

These tumours are nowadays principally recognized by their histological staining patterns, due to shared cellular proteins. Silver staining was historically used, and tumours were classified as showing an argentaffin reaction if they took up and reduced silver, and being argyrophilic if they reduced it. At present, immuno-cytochemical localization of chromogranins (A, B, C), neuron-specific enolase, and synaptophysin which are all neuroendocrine cell markers, are used.

Apudomas, pathologically, are neoplastic endocrine lesions which take the form of adenoma, adenomatous hyperplasia or carcinoma. Ultra-structurally, these tumours possess electron-dense neuro-secretary granules (> 80 nm) and frequently contain small clear vesicles. They synthesize numerous peptides, growth factors and bioactive amines that may be ectopically secreted, giving rise to clinical syndro-

mes. However, the presence or absence of clinical syndrome or type cannot be predicted by immune-cytochemical studies and instead need clinical correlation.

These tumours are generally slow growing, but some can be aggressive - most are well-differentiated having low proliferative indices. Histological classifications (grading, TNM staging) have prognostic significance with only invasion or metastases establishing malignancy.

Recent advancements in classification and clinical syndromes associated with apudomas

Apudomas, currently termed as neuroendocrine tumours (NETs) are broadly divided into gastrointestinal NETs (GI-NETs) and pancreatic NETs (pets). GI-NETs are classified based on their anatomical area of origin, for instance, foregut, midgut and hindgut.

Foregut tumours generally have a low serotonin content; are argentaffin-negative but argyrophilic; occasionally secrete adrenocorticotropic hormone (ACTH) or 5-hydroxytryptophan (5-HTP); causing an atypical carcinoid syndrome; are often multi-hormonal and may metastasize to bone. Midgut tumours are argentaffin-positive, have a high serotonin content, most frequently cause the typical carcinoid syndrome when they metastasize as they release serotonin and tachykinins (substance P, neuro-peptide K, substance K), and rarely ACTH or 5-HTP. Hindguts carcinoid is argentaffin-negative, often argyrophilic, rarely contain serotonin or cause the carcinoid syndrome.

The cardinal features of carcinoid syndrome associated with GI-NETs include flushing and diarrhoea. The characteristic flush is of sudden onset and is a deep red or violaceous erythema of the upper body, often associated with a feeling of warmth and occasionally associated with pruritus, lacrimation, diarrhoea and facial oedema. Diarrhoea is usually watery and associated with steatorrhea and abdominal pain. Cardiac manifestations may occur due to formation of fibrotic plaques involving the endocardium, resulting in tricuspid inefficiency, tricuspid stenosis and pulmonary inefficiency, eventually leading to heart failure.

While serotonin, one of the main secretary products of GI-NETs, stimulates increase in intestinal motility and fibrogenesis, tachykinins are released during flushing. Moreover, serotonin uses up to 50% of dietary tryptophan for its synthesis and leads to formation of pellagra-like lesions due to niacin deficiency. The diagnosis relies on measurement of urinary or plasma serotonin or its metabolites in urine, 5-HIAA being used most frequently.

Treatment includes avoiding conditions that precipitate flushing, dietary supplementation with nicotinamide, treatment of heart failure with diuretics, treatment of wheezing with oral bronchodilators and control of diarrhoea with anti-diarrhoeal agents like loperamide. If patients are still symptomatic, somatostatin analogues or serotonin-receptor antagonists like octreotide and lanreotide are drugs of choice.

Surgery is the only potentially curative therapy. The probability of metastatic disease increases with increasing size in most GI-NETs, so the extent of surgical resection must be determined accordingly. With appendiceal NETs < 1 cm, simple appendectomy is curative; with rectal NETs < 1 cm, local resection is curative; but in small intestinal NETs, a wide resection with en bloc resection of adjacent lymph-bearing mesentery is recommended. If the tumour is > 2 cm in any case, a full cancer operation (right hemicolectomy for appendiceal NETs, abdominoperineal resection or low anterior resection for rectal NETs and an en bloc resection of adjacent lymph nodes for SI-NETs) must be done.

With type I or II gastric NETs < 1 cm, endoscopic removal is recommended; but in tumours > 2 cm or in case of local invasion, total gastrectomy is recommended. With type III gastric NETs > 2 cm, excision and regional lymph node clearance are recommended.

pNET are classified into nine well-established specific functional syndromes, six additional very rare specific functional syndromes, five possible specific functional syndromes and non-functional pNET. Functional pNET usually present clinically with symptoms due to the hormone-excess state while prominent symptoms like abdominal pain are seen only late in the course of the disease. On the contrary,

all symptoms in non-functional pNET are due to the tumour. Moreover, many of these symptoms are not recognized and thus they are missed. This gives an incomplete picture of the cases.

The well-established functional pNET syndromes with the tumour location and the biologically active peptide secreted are as follows:

- Zollinger-Ellison Syndrome in which the tumour is located in duodenum and pancreas; and gastrin is secreted.
- Insulinoma in which the tumour is located in pancreas; and insulin is secreted.
- Varner-Morrison Syndrome in which the tumour is located in pancreas; and Vaso-active Intestinal Peptide are secreted.
- Glucagonoma in which the tumour is located in pancreas; and glucagon is secreted.
- Somatostatinoma in which the tumour is located in pancreas and duodenum/jejunum; and somatostatin is secreted.
- ACTHoma in which the tumour is located in pancreas; and ACTH are secreted.
- GRFoma in which the tumour is located in pancreas, lungs and jejunum; and Growth Hormone Releasing Hormone are secreted.
- pNET cau
- sing carcinoid syndrome in which the tumour is located in pancreas; and serotonin and tachykinins are released.
- pNET causing hypercalcemia in which the tumour is located in pancreas in which PTHrP is secreted.

The tumours are mostly located in pancreas in case of rare specific functional syndromes and possible specific functional syndromes with a variety of peptides ranging from rennin, luteinizing hormone and erythropoietin to calcitonin, neurotensin and ghrelin secreted.

Some functional pNET present with severe symptoms with a small or undetectable primary tumour, whereas non-functional tumours usually present late in disease course with large tumours, which are frequently metastatic.

Treatment of pNET requires two different strategies. Firstly, it must be directed at the hormone-excess state such as the gastric acid hypersecretion in gastrinomas or hypoglycaemia in insulinomas. Ectopic hormone secretion usually causes the presenting symptoms and can cause life-threatening complications. Secondly, with all the tumours except insulinomas, more than 50% are malignant; hence, treatment must also be directed against the tumour. Surgical resection is curative but it is often not possible as there is presence of an advanced disease at the time of diagnosis in most cases, due to which surgery is no longer possible in such patients.

Cytoreductive surgery is considered if at least 90% of the visible metastatic disease is thought to be resectable. Radiofrequency ablation can be used in case of hepatic metastases. Chemotherapy is widely used in advanced pNET, unlike in GI-NETs where it has a poor response rate. The regimen of choice for patients with well-differentiated pNET include a combination of streptozocin and doxorubicin with or without 5-fluorouracil.

Long-acting somatostatin analogues like octreotide and lanreotide are effective in controlling the functional hormonal state, as well as have anti-proliferative properties. Interferon α plays a similar role by inhibiting DNA synthesis, blocking cell cycle progression, inhibiting protein synthesis and angiogenesis, thereby inducing apoptosis.

Selective internal radiation therapy using yttium-90 glass or resin microspheres is a relatively newer approach being evaluated in patients with unrespectable NET liver metastases. Molecular targeted medical treatment with either an mTOR inhibitor (everolimus) or tyrosine kinase inhibitor (sunitinib) is a newer approach, only recently approved in the United States and Europe [1-13].

Conclusion

The incidence of Apudomas is less common that of adenocarcinomas of the gastrointestinal tract, but it has slowly been on the rise in the last 30 years. Both GI-NETs and pNET commonly show malignant behaviour and the presence of liver metastases is the single most important prognostic factor in determining survival and the aggressiveness of the tumour. It is imperative that an index of strong suspicion

is necessary to get a comprehensive presentation and institute appropriate treatment to mitigate the disadvantages for a better outcome.

A number of diseases due to various genetic disorders are associated with an increased incidence of neuroendocrine tumours or Apudomas, due to loss of a possible tumour-suppressor gene, most important of which is Multiple Endocrine Neoplasia type I (MEN-1). The presence of molecular alterations correlates with tumour growth, tumour size, and disease extent or invasiveness, in turn playing a huge role in the prognosis.

Since the advent of the APUD concept by Pearse in early 1960s, the domain of information regarding the presentation, patho-physiological peculiarities as well as treatment modalities for Apudomas or neuroendocrine tumours have gradually extended; yet it continues to be one of the most mystifying neoplastic lesions of the gastrointestinal tract.

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