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Review

Goblet cell appendiceal tumors – Management dilemmas and long-term outcomes

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ABSTRACT

Background: Appendiceal Goblet cell tumors (GCT_s) are clinically more aggressive, and have a worse outcome than midgut neuroendocrine tumors (mNETs). Guidelines for management of GCTs are limited.
Methods: A retrospective case-study analysis was performed in patients with a diagnosis of GCT, confirmed on histological review. Patients were evaluated clinically, biochemically, and radiologically.
Results: 48 patients were identified (TNM stage I–II: 27, stage III: 15, stage IV: 6). Median follow-up was 44 months and was complete in all patients. 68.8% presented with acute appendicitis. 44/48 patients had initial appendectomy, followed by prophylactic right hemicolectomy in 41. 10/48 patients had recurrent disease [median time to recurrence 28 months (range 4–159)]. Of those, 9 received systemic chemotherapy (FOLFOX/FOLFIRI), which was also given in 5/48 patients with disseminated disease at diagnosis. Partial response, stable disease and disease progression was noted in 22%, 22% and 56%, respectively. Adjuvant chemotherapy was also administered in 9/48 patients with stage III disease after right hemicolectomy, however in 3/9 the disease recurred. Median progression/disease-free-survival was 44 months (range 3–159) and overall 5-year survival rate was 41.6%.
Conclusions: The clinical behaviour of GCTs is more similar to colorectal adenocarcinomas than to NETs. A prophylactic right hemicolectomy is recommended to reduce the risk of recurrence. Systemic chemotherapy, using colorectal adenocarcinoma regimens, is indicated for advanced or recurrent disease and has encouraging results. Prospective studies are needed to define the role of adjuvant chemotherapy and the optimal chemotherapy regimen.

Contents

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Introduction

Goblet cell tumors (GCTs) are a rare subtype of mixed adeno-neuroendocrine carcinomas (MANEC) [1], being considered a distinct entity from appendiceal neuroendocrine (carcinoid) tumors (NETs) and are clinically more aggressive. GCTs occur in 0.3%–0.9% of appendectomies and comprise 35%–58% of all appendiceal neoplasms [2–5], and less than 14% of all malignant tumors of the appendix [6].

These tumors were first described in 1969 by Gagne et al. [7], whereas the term goblet cell appendiceal carcinoids was introduced by Subbuswamy et al. in 1974 [8], because the predominant cell type was thought to be similar to the normal goblet cell of the epithelium of the intestinal tract.

GCTs almost exclusively occur in the appendix but may occasionally be found in other regions of the gastrointestinal tract [9,10]. They are usually diagnosed incidentally during appendectomies or ileocaecal resection. The mean age at presentation is 52 years, 10 years later than that of those with appendiceal NETs, but approximately 10 years earlier than that for jejuno-ileal NETs [1]. A gender preference has not been reported in GCTs [6,11–13], while an ethnic preference for Caucasians is clearly observed as more than 80% of GCTs have been reported to occur in this subgroup in the Surveillance, Epidemiology and End Results (SEER) database [6,12]. Jiang et al. described a series of appendiceal GCTs from China [14] and found that schistosomiasis might be a potential risk factor for GCTs.

Up to 60% of the patients present with acute appendicitis [15,16] and, in this scenario, GCTs often involve the total length or, less commonly, only the base of the appendix [17]. In cases with disseminated disease, abdominal pain associated with an abdominal mass and weight loss may be the first symptom at presentation [13].

The overall 5-year survival for GCTs ranges between 40 and 75% [11–13] in those cases with loco-regional spreading, whereas a poorer outcome has been reported for metastatic disease (overall 5-year survival rate < 20%) [11–13].

The pathogenesis of GCTs is still a matter of debate; in fact, some authors attribute the development of these tumors to the occurrence of p53 mutations and G:C to A:T transitions, both consistent with a defect in DNA repair [18], whilst other studies suggest that allelic loss of chromosomes 11q, 16q, and 18q is a frequent occurrence in GCTs [19].

Due to their rarity, data on GCTs are scarce and the European Neuroendocrine Tumor Society (ENETS) 2012 guidelines mainly represent an expert opinion based on retrospective analysis of the available literature [1]. Accordingly, many issues concerning the management of GCTs remain to be elucidated.

We present a series of GCTs, which includes long-term follow-up data and is focused on clinical manifestations, diagnosis, and treatment. An algorithm for GCT management is also proposed.

Methods

Patients with a histologically confirmed diagnosis of GCT, who were diagnosed and treated from 1996 to 2013, were identified from our database at the Neuroendocrine Tumor Unit, Royal Free Hospital, London, United Kingdom. The histopathological material from all tumors was retrospectively re-reviewed, by an expert Gastro-Intestinal/Neuroendocrine Tumor Histopathologist.

Histology

Goblet cell tumors were classified according to Tang's classification [13] in group A, i.e. typical goblet cell carcinoid tumors; group B, i.e. adenocarcinoma ex goblet cell carcinoid tumor, Signet Ring Cell Type and group C, i.e. adenocarcinoma ex goblet cell carcinoid tumor, poorly differentiated adenocarcinoma type.

As GCTs have historically been considered as a sub-type of NET, the Ki-67 proliferative index (which determines the proportion of tumor cells actively dividing) was determined in histopathological tumor specimens. The WHO classification 2010 divides NETs into three groups with different biological behaviour [20]. Tumor size was estimated on histopathological samples according to TNM classification [21,22].

Table 1 summarises all histological classifications that have been used for GCTs.

Biochemical and radiological assessment

Initial evaluation and follow-up of patients included cross-sectional imaging, consisting of triple-phase computed tomography (CT) or magnetic resonance (MRI) scan and biochemical assessment including tumor markers [carcinoembrionic antigen (CEA), CA-125, CA 19-9, CA15-3, alphafetoprotein (AFP)] which were measured at diagnosis and during follow-up. In addition, whenever available, plasma chromogranin-A (CgA) and chromogranin B values were recorded. CgA values (both A and B) as well as tumor markers were ranked in 4 groups: normal or with an increase of less than 2 times the upper limit of normal (ULN), between 2 and 5 ULN, higher than 5 times ULN, respectively.

The follow-up protocol included contrast CT or MRI as well as biochemical markers at six month interval for the first five years, and yearly thereafter. Data on functional imaging [111-Indium pentetreotide scintigraphy (OctreoScan), Gallium-68- Octreotate Positron Emission Tomography (PET) scan and/or Fluorodeoxyglucose(FDG)-PET scan, performed at diagnosis and in the case of suspicion of disease progression, were also recorded.