A Coexistence of Epithelial and Mesenchymal Neoplasm in A Tertiary Health Care Center. Synchronous Tumor in Gastro-Oesophagectomy Specimens- A Retrospective Analysis

Zahida Niaz*, Ramesh Babu, Abdullaha Al Rawahi, Babikir Ismail, Nausheen Yaqoob, Ibrahim Al Haddabi, Asma and Hazwa Al Rafa Polyclinic International City, Muscat, Sultanate of Oman

*Corresponding author:
Zahida Niaz,
Al Rafa Polyclinic International City, Muscat,
Sultanate of Oman

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1. Abstract
We are describing three cases of simultaneous occurrences of an epithelial lesion with a mesenchymal lesion in the gastrointestinal tract. The synchronous occurrences in first case are with oesophageal squamous cell carcinoma and gastrointestinal tumor, second case is oesophageal adenocarcinoma with gastrointestinal tumor, and third case is oesophageal squamous cell cancer and gastric leiomyoma. The synchronous occurrence of GIST, gastric leiomyoma and other primary tumours is more common than it has been considered in the past decades. Further studies are needed to analyze the correlation between the synchronous occurrence of GIST, gastric leiomyoma, and other primary GI neoplasms.

2. Introduction
Synchronous tumour indicates the presence of two or more primary tumours diagnosed simultaneously (or) within 6 months to each other [1]. Also simultaneous occurrence of an overlying epithelial and mesenchymal lesion is exceedingly rare. Oesophageal cancer (OC) is the most common epithelial tumour of the oesophagus [2]. It is the ninth most common cancer diagnosed globally yet the sixth most common cause of cancer related death [3]. There are two major subtypes, oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC), for which OSCC is estimated to contribute 70% of all oesophageal cancer diagnosed globally [4,5]. With better treatment options survival of patients with oesophageal cancer has improved over the last years but the risk of developing multiple primary tumours (MPTs) have increased [6]. These MPTs will affect the prognosis, survival of patients with OAC and the choice of OAC treatment in case of synchronous second primary tumour (SPT) detection [7]. Hence, it is important that we detect MPTs at an early stage when curative treatment is still possible. Most common mesenchymal tumours of the stomach are gastrointestinal tumours (GISTs) [8,9]. GISTs commonly co-exist with other primary tumours, which can either involve the GI tract or other extra-GI sites and synchronous occurrence varies from 4.5% to 33%. The most frequent localization being the GI tract [10]. It is not yet clear if there exists a causal association for the concomitant occurrence of GIST with other malignancies or if this is merely coincidental. Approximately 2.5% of all the gastric neoplasms represent gastric leiomyomas [11]. Gastric submucosal tumours are often asymptomatic and they are usually discovered incidentally while doing routine upper gastrointestinal endoscopy. Gastric leiomyomas share many characteristics with GISTs, but GISTs have malignant potential [12,13]. So here we shall describe three cases having synchronous occurrences of an epithelial lesion with a mesenchymal lesion. The synchronous occurrences in first case is with oesophageal squamous cell carcinoma and gastrointestinal tumour, second case is oesophageal adenocarcinoma with...
gastrointestinal tumour and third case is oesophageal squamous cell carcinoma and gastric leiomyoma.

3. Materials and Method
We have received three case of co-existence of Retrospective analysis of esophageal resection from March 2022 to March 2023, Department of histopathology, Sultan Qaboos Comprehensive Cancer Centre, Oman. The clinical details are recovered from the hospital records.
4. Results

4.1. Case 1

A 70 year old male was referred to our hospital with history of dysplasia, loss of appetite and weight loss. On endoscopic evaluation, there was a friable nodular ulcerated tumour seen 25cm from the incisor, covering two third of the circumference extending down till 38 cm causing narrowing of the lumen. Yet the scope passed smoothly to the stomach. In stomach, antrum showed large non-ulcerated round submucosal lesion with normal overlying mucosa measuring 4 x 4cm. Positive emission topography scan showed large asymmetric wall thickening with mass formation involving the upper, mid and lower thoracic oesophagus with FDG avid right supraclavicular, upper periesophageal / superior mediastinal and right upper paratracheal lymph nodes showed likely to be metastatic. Stomach showed a round non FDG avid mass in the antrum. Biopsy of oesophageal lesion and gastric lesion was done followed by resection of the gastric mass and esophageal resection. Histo-pathology: Oesophageal biopsy showed tiny fragments of severely ulcerated, partly necrotic and inflamed oesophageal mucosa infiltrated by a poorly differentiated malignant tumour composed of nests and cords of malignant cells showing pleomorphic hyperchromatic nuclei with scant cytoplasm and focal glandular formation. A tiny intact mucosa shows probably epithelial atypia. No perineural or lymphovascular invasion was identified. Focal papillary like pattern is also noted. Adjacent stroma shows desmoplasia and lymphoplasmacytic infiltrate. Immunohistochemistry report showed p40 positive with CK7 and PDL1 negative in tumour cells. Section from the gastric biopsy showed a well encapsulated gastrointestinal stromal tumour. The tumour cells were seen to be arranged in fascicles and bundles and was separated by thin fibrovascular septae. The cells are spindle to epitheloid shape with vesicular nucleus, uniform chromatin with prominent nucleoli in some and with moderate eosinophilic cytoplasm in some. There are paranuclear vacuoles. Mitosis is low (1/50 hpf). Few areas of hyalinization noted. No necrosis seen. The biopsy also showed Helicobacter Pylori positive. Immunohistochemistry showed CD117 and DOG positive with patchy positive for SMA and negative for CD34 and S100. Ki67 proliferation index of GIST was low. Patient was treated for oesophageal carcinoma with chemotherapy – 5 flurouracil and oxaliplatlin.

4.2. Case 2

A 77 year old male, known case of atrial fibrillation on medication (Rivarox and Bisoprolol with Proton Pump Inhibitor) and referred to the centre as diagnosed case of oesophageal adenocarcinoma, stage T2N0,4cm away from the gastro-oesophageal junction and was planned for pre-operative chemo-radiation according to CROSS trial. Echo was normal and currently he had normal sinus rhythm. COVID related pericarditis was noted and was on Colchicine medication. Endoscopy report showed a small gastric inlet in the upper oesophagus with normal mucosa. In distal oesophagus at 32cm from incisor there is a non-obstructing fungating ulcerated tumour covering 2/3 rd of the mucosa with a length of 4cm, reaching down to 36cm. Gastro-oesophageal junction is at 38cm and is
not involved by the tumour. Patient had received two cycle dose of chemotherapy (Paclitaxel/Carboplatin). Consecutive cycles were not given due to neutropenia. Three week radiotherapy was given and underwent surgery Ivor Lewis procedure. Histopathology report was given as sections from the area of mucosal foldings showed inflammation and fibrosis with focal erosions distally. No evidence of malignancy. There is a small focally ulcerated gastric polyp with few dilated glands. Stomach focally shows mucosal congestion. Mucosa at gastro-oesophageal junction shows focal ulceration with severe inflammation, endothelial proliferation and adjacent epithelial atypia of probable reactive nature (levels seen). The proximal resection margin shows basal acantholytic change with basal dysplasia. There is also mixed acute on chronic inflammation extending to muscle and around submucosal blood vessels. Some of the submucosal ducts shows squamous metaplasia. There is also mild fibrosis of the submucosa. No evidence of malignancy. Distal resection margin is unremarkable. A small, encapsulated and well circumscribed spindle cell nodule (0.4cm) is retrieved from the submucosa fat. This showed features of small gastrointestinal tumour. Immunohistochemistry showed positive staining for SMA and CD117 and negative for CD34. This profile confirmed gastrointestinal tumour. No atypical features were noted. Histomorphology showed complete response to primary oesophageal tumour, acute on chronic inflammation, ulceration, fibrosis and congestion. Nine lymph nodes were identified and were free of tumour.

4.3. Case 3

A 63 year old, female patient, diagnosed with distal oesophageal local advanced squamous cell carcinoma had chemo-radiation based on CROSS trial protocol. Computed tomography scan showed good partial response at the tumour site with no signs of distant metastasis. She had minimally invasive Ivor Lewis oesophagectomy with intrathoracic oesophageo-gastrostomy frozen sent for proximal margin of surgical resection. Endoscopy was done and the Pentax EUS radial scope was passed under direct vision to lower oesophagus. Time was spent in evaluating the oesophageal tumour. In the distal oesophagus at 32cm from the incisors there was a fungating non-obstructing tumour reaching down to 36cm. EUS evaluation showed tumour extending from mucosa up to muscularis propria with intact adventitia. There was no regional enlarged lymph nodes. EUS staging was given as T2NO. Oesophagectomy with oesophago-gastrostomy resection was done. Frozen section from the proximal margin of oesophagectomy specimen showed negative for dysplasia or malignancy. Sections from the esophagus showed normal stratified squamous epithelium with no evidence of residual carcinoma (complete pathologic response). Focal mild reactive atypia is noted. However, there is no evidence of dysplasia or invasive malignancy. Focal areas show treatment related changes with mild fibrosis, vascularization, few collections of foamy macrophages and scattered hemosiderin pigments. There is no evidence of lymphovascular or perineural invasion. Sections from the gastric tissues showed multiple submucosal well-defined varying sized nodular spindle cell lesions. The cells are arranged in fascicles and short bundles. They exhibit elongated vesicular nuclei and moderate eosinophilic cytoplasm. Sections from remaining gastric mucosa appear unremarkable. Distal resection margin is negative for dysplasia or malignancy. Seventeen lymph nodes were identified from the surrounding soft tissue which were negative for metastatic tumour. Final impression was given as oesophagectomy proximal margin and distal resection margin was free of tumour and there was no evidence of residual tumour. Multiple gastric leiomyoma was seen.

5. Discussion

Gastric leiomyomas are a rare type of gastrointestinal mesenchymal tumour and most commonly arise in the muscularis propria or muscularis mucosae of the stomach [14]. This feature is also common with GISTs, making them hard to differentiate [15]. GISTs generally have malignant potential and can develop metastases [16]. The main issue in asymptomatic patients with gastric submucosal tumours is that we have to determine whether or not the tumours have malignant potential [16] and hence necessity for resection. Mazur and Clark first coined term GIST [17]. Although they account for only about 0.1–3% of all GI malignancies, they are the most common mesenchymal tumours of the GI tract. They can arise anywhere along the GI tract with the most preferred location being gastric in about 60% of the cases [18]. GISTs are composed of spindle (70%) or epitheloid (20%) cells or can be mixed. They are usually positive for immunostains CD34, c-Kit (CD117) and DOG [19]. DOG1 which was discovered in 2004 is a sensitive and specific marker for detecting GISTs of gastric origin [20]. Many GISTs are diagnosed after the onset of clinical symptoms which includes abdominal mass, pain, and bleeding [21]. However, occasionally they can also be discovered incidentally during the evaluation of other clinical entities [22]. GIST and other primary GI tract neoplasms are distinct tumours which is seen to originate from different cell layers and synchronous development is quite uncommon [23]. The percentage of GIST with other diagnosed neoplasms is reported to range between 3 and 33% [24]. Concurrent occurrence of GIST and GEJ neoplasms is quite rare and literature reports only few cases [25]. Spinelli et al. had reported a case of lower third of oesophagus squamous cell carcinoma with an incidental pathologic diagnosis of a concomitant GIST in the thoracic tract [26]. Also, Hsiao et al. had reported a concurrent GIST and GEJ adenocarcinoma [25]. In addition, case series by Chan et al. had documented cases with coexistence gastric GISTs with GEJ adenocarcinomas [27]. Synchronous occurrence of gastric epithelial and stromal tumor raises the question whether such an occurrence is simply a coincidence or can the two lesions be related to a certain etiology [28]. Various hypotheses have been proposed regarding this simultaneous presentation, which included gene mutation, expression of metallothionein’s and H. pylori infection.
that may have promoted proliferation of different cell lines, while some other authors considered the possibility of sporadic occurrence. Currently, there is no strong data to support these hypotheses [25, 19, 28]. Some researchers believed there is an existence of a certain carcinogen that can act on different tissue cells in the same or adjacent organs and that can result in two types of tissue differentiation. However, some researchers also reported that there was no existing relationship between the synchronous occurrence of these two tumours and this phenomenon is simply coincidental [29].

6. Conclusion

In conclusion, the synchronous occurrence of GIST, gastric leiomyoma and other primary tumours is more common than it has been considered in the past decades. Majority of them are being found incidentally during surgery which is performed for another malignancy. Surgeons should be vigilant in recognizing a coexisting tumor before or during surgery and should be prepared to modify the surgical plan accordingly. Further studies are needed to analyze the correlation between the synchronous occurrence of GISTs, gastric leiomyomas and other primary GI neoplasms. Even though coincidence may be the answer, the hypothesis of gene mutations or the same carcinogenic agent resulting in two tumours of different origin cannot be excluded.

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