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Original Research Paper

Oncology

AN EXTREMELY RARE ASSOCIATION BETWEEN PRIMARY ILEAL DIFFUSE LARGE B CELL LYMPHOMA AND CARCINOID TUMOR.

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ABSTRACT

Introduction: The incidence of synchronous multiple primary malignancies, though rare, is increasing due to advancements in cancer therapy and screening protocols. Here, we present a case of a 50-year-old male with appendiceal carcinoid tumor and ileal diffuse large B-cell lymphoma. **Case Report:** A 50-year-old male presented with severe abdominal pain, nausea, weight loss, and anaemia. CT scan revealed a circumferential thickening in the terminal ileum with a polypoidal extension and a retroperitoneal mass. Emergency surgery revealed a large tumor involving the ileum and a mesenteric mass. Histology confirmed Diffuse Large B-cell Lymphoma in the ileum and Carcinoid in the appendix. **Discussion:** Primary GI non-Hodgkin lymphoma is rare, often overshadowed by secondary metastases. Carcinoid tumors, increasing in incidence, seldom associate with lymphoreticular cancers. Patients with carcinoids have high rates of second primary malignancies, challenging management. The aetiology thology remains unclear, possibly involving neuroendocrine peptides and shared signalling molecules with lymphoreticular tumors. **Conclusion:** Our article demonstrated an unusual association between DLBCL and an appendiceal carcinoids that highlights the significant role of histological and immunohistochemical staining in confirming the diagnosis.

KEYWORDS :

INTRODUCTION

The incidence of multiple primary malignancies in a single patient has grown over last ten years, despite being a rare occurrence. First report of double primary in single patient was made more than a century ago. Since then, this phenomenon has been identified with increasing frequency, in part due to increase in life expectancy of cancer survivors, a boon of advancements in cancer therapeutic and to more comprehensive screening protocols used in cancer patients. The two cancers are either detected at same time (synchronous) or one may follow the other after a period of time (metachronous). [1] Prevalence of multiple primary malignancies worldwide is 0.734–11.7%. There are 14–20% of patients with primary malignancy with higher risk to experience multiple primary malignancies affecting their quality of life. [2-4]. Carcinoid tumours of gastrointestinal tract, have a tendency to occur at multiple sites, and are frequently associated with tumours of other types. These tumours are mostly adenocarcinomas of the gastrointestinal tract, but tumours of various other types and locations have been described [5-6]. Very few reports exist of carcinoid tumours with lymphoreticular system cancers, particularly those involving appendix carcinoid tumours.

In this paper we report synchronous occurrence of a carcinoid tumour of appendix and a non-Hodgkin's lymphoma of ileum. This combination of tumour types, to the best of knowledge, is the fourth case to be reported worldwide.

Case Report

We report a case of a 50-year-old male who presented to the emergency of our hospital due to a severe, persistent abdomen pain accompanied by nausea, vomiting and melena. Patient also gave history of anorexia and significant weight loss. There was no past surgical history, drug, and allergic histories. Patient was diabetic on medications. His father died of an oral malignancy. Physical examination revealed a soft, non-tender abdomen. A mass was palpable in right iliac fossa.

Lab findings were significant for anaemia with a haemoglobin level of 8g/dl.

An abdominal and pelvic computed tomography scan demonstrated an ill-defined enhancing circumferential wall thickening in terminal ileum with a polypoidal extension for a segment of 6 cm with perilesional nodule and a large deposit poster inferior to right kidney in para-aortic region, measuring ~ 5.5 x 5.0 cm. There was no evidence of small bowel obstruction. Few heterogeneously enhancing lesions were seen in mesentery in right lumbar region, largest measuring 5 x 4.5 cm (Figure 1).

Patient underwent emergency ileal resection with ileoascending anastomosis, through which a retroperitoneal mass was removed as well as part of ileum and appendix.

Gross examination showed a specimen measuring 30x12x5cm consisting of terminal ileum, caecum, appendix and ascending colon. Terminal ileum measured 16x2 5 cm, caecum measured 6x6 cm, appendix measured 5x1cm and ascending colon measured 11x4 cm. Total mesorectal excision was nearly complete. A polypoid tumor measuring 7 x 4.5x3.5 cm was identified involving the terminal ileum and mesenteric mass. Tumor grossly appeared to involve muscularis propria. Tumor site perforation was not seen. Adjacent mucosa was unremarkable. Appendix was grossly unremarkable (Figure 1).

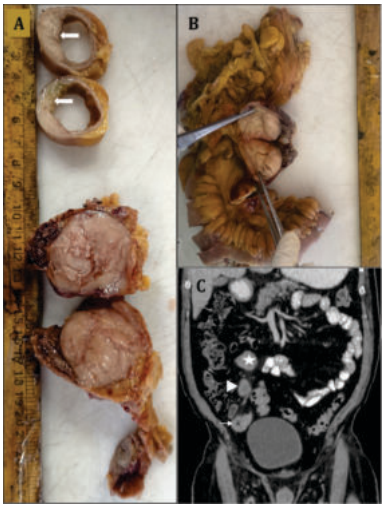

Figure 1: (A) Gross image shows a circumferential wall thickening of the terminal ileum (white arrows) with a

mesenteric mass (below) measuring 6X4X3 cm. (B) A polypoidal tumor measuring 6x4.5x3.5cm is identified involving the mesentery. Cut section of the tumor was grey-white, solid, and homogenous. (C) Coronal contrast enhanced CT image shows an enhancing polypoidal mass within the appendix (block arrow) and enhancing circumferential wall thickening of the terminal ileum (line arrow). Enhancing nodal mass is seen in the mesentery (star).

Microscopic examination of ileal mass and mesenteric mass showed a malignant round blue cell tumor consisting of sheets of medium to large sized atypical lymphoid cells infiltrating the submucosa. Individual cells showed pleomorphic round to oval to nuclei, coarse chromatin, conspicuous nucleoli and scant cytoplasm. Brisk mitosis was noted.

Necrosis is present. Lymphatic emboli are not identified. Vascular emboli were not identified. Perineural invasion was not identified. Adjacent colon was unremarkable. On immunohistochemistry, the tumor cells were positive for CD20, MUM 1, BCl6, Ki67-mib1 (90% of tumor cells); negative for Tdt , CD3 , CD10. ~15-20% cells show nuclear positivity for c-myc (Figure 2).

On the other hand, the histological examination of the appendix showed nests of tumor cells infiltrating the appendiceal stroma. These tumor cells had round monomorphic nuclei, stippled chromatin and moderate eosinophilic cytoplasm. Mitosis was < 2 mitoses / 2 cumm.

On immunohistochemistry these tumor cells were positive for INSM-1, chromogranin, CD56 and synaptophysin. Ki67 proliferative index is <1% (Figure 3).

Total eighteen regional Lymph Nodes were dissected which were free of tumor.

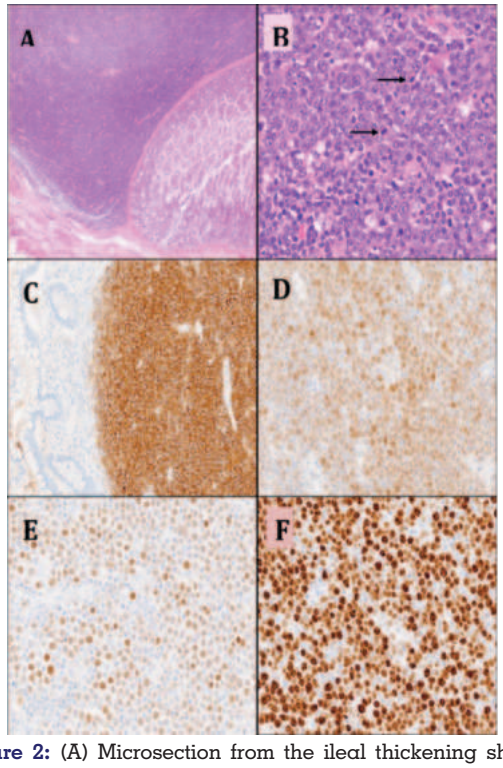

Figure 2: (A) Microsection from the ileal thickening shows sheets of tumor cells in the submucosa. Normal mucosa is seen on the bottom right, (H&E, 10X). (B) Higher magnification shows large-sized atypical lymphoid cells, having coarse chromatin and frequent mitotic figures (arrow), (H&E, 40X). (C) Tumor cells are diffusely positive for CD20. (D) MUM-1 is positive. (E) Bcl6 is positive in >30 % of the tumor cells. (F) The MIB-1 labelling index is ~ 85%.

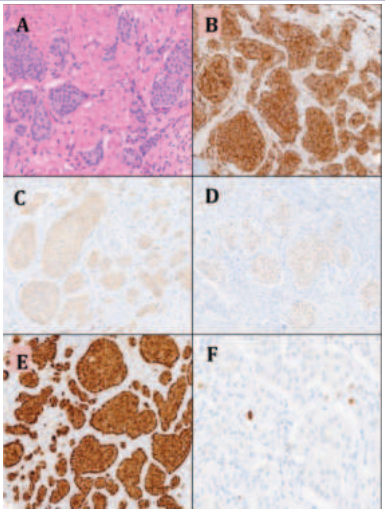

Figure 3: (A) Section from the appendix shows nests of tumor cells having uniform round nuclei, salt and pepper chromatin and moderate cytoplasm, (H&E, 40X). (B) Tumor cells are positive for CD56. (C) Synaptophysin is positive. (D) INSM-1 shows nuclear positivity. (E) Chromogranin shows strong and diffuse positivity. (F) The MIB-1 labelling index is <1 %.

Thus, a final diagnosis of Diffuse Large B-cell lymphoma, post germinal centre B-cell phenotype, high grade was made in terminal ileum and Carcinoid of appendix.

Postoperatively the patient had to be transfused with 3 unit PRBC on account of anaemia and was treated with antibiotics for surgical site infection. Gradually the patient recovered and was discharged.

After the final report of histopathological examination was released patient was planned for chemotherapy and was started with RCHOP regimen.

A retrospective review of previous CT scan was performed in order to identify the lesion in appendix which showed a polypoidal mass arising from appendix.

DISCUSSION

Primary GI non-Hodgkin lymphoma is considered a rare entity, affecting 10-15% of all NHL patients and accounting for only 1-4% GI neoplasms. Gastrointestinal system is the most common site for extra-nodal NHL. Adolescent populations are among rarest of compromised groups, especially males. Gastrointestinal system is more involved by secondary metastasis rather than by primary lymphomas [7].

Carcinoid tumors on the other hand account for 0.66% of all malignancies, as per The Surveillance Epidemiology and End Results (SEER) database from 1973 to 2004. In contrast to all other malignancies with steady incidence rates, carcinoid tumors are increasing by 3-10% per year according to SEER database [8,9].

The correlation between GI carcinoids and other tumors have been frequently reported, such as adenocarcinoma, squamous cell carcinoma, gliomas, mesotheliomas, urothelial carcinomas, hepatomas and leiomyosarcomas. However, there have been few reports of carcinoid tumors being associated with lymphoreticular system cancers [10]. According to literature, there are eight case reports of carcinoids with associated lymphoreticular system malignancies; two of these cases involved non-Hodgkin lymphomas of the GI tract, while the topographical location was not mentioned in four cases. Appendiceal carcinoid malignancies in association with lymphoreticular cancers till date have been reported only thrice, ours being the fourth case (Table no 1).

Table 1: Previously Reported Cases Of Appendiceal Carcinoid Tumors Associated With Lymphomas

Authors and year of publication	Reference number	Case no.	Associated lymphoma	Location	Treatment plan	Patient follow up
Foreman (1952)	7	1st case	Lymphosarcoma	N/M	N/M	Followed up for 26 months: weight loss and intermittent diarrhoea present.
Lindboe (1999)	17	2nd case	T cell lymphoma	Ileum	CHOP regimen	Last follow up August, 1998(10 months): Uneventful.
Kherbek (2023)	18	3rd case	Burkitt lymphoma	Enteric segment	Alternating sessions of R-CHOP and methotrexate, then courses of cytarabine and methotrexate.	Patient will be followed at periodic intervals of 3 months for the first 2 years. Then at intervals of 6 months for the next 3 years.
Present case	-	4th case	Diffuse large B cell lymphoma	Ileum	R-CHOP for DLBCL No chemo for carcinoid	Last follow up May 2024: Uneventful

A synchronous second primary malignancy in a patient in whom an uncommon neoplasm has been diagnosed is difficult to detect, particularly when the clinical patterns of the two neoplasms overlap. In our case a second primary was not suspected clinically or radiologically, until it became obvious at the time of morphological examination. Our patient, a 50-year male presented with an ileal mass with mesenentric spread and was incidentally diagnosed with carcinoid tumour of appendix.

According to several large series of patients with primary gastrointestinal carcinoids, incidence of second primary malignancies (SPM) can exceed 50%, gastrointestinal carcinoids show that the rate of SPM ranges from 12-46%, with an average of 17%. These figures are astounding, considering that estimated rate of SPM associated with other malignancies is 2.3% in surgical cases and 8.1% in autopsy cases.

Small-bowel carcinoids have highest rate of SPM (29-52%), followed by appendiceal (13-32%) and colorectal carcinoids (5-32%), however presenting symptoms mostly referable to the second primary, not the carcinoid, because the second primary is usually the more aggressive malignancy. Most carcinoid patients with a second malignancy do not die from carcinoid tumor but from the second tumor. [5,10].

The cornerstone of carcinoid management is to achieve complete resection of all tumor cells. In cases where curative surgery is not possible, debulking surgery, radiofrequency ablation, hepatic artery embolization, somatostatin analogues, or chemotherapy are all options to achieve symptom and biochemical control [9]. Managing two distinct malignancies at the same time is the key challenge. Hence, an optimal treatment plan using surgery or chemotherapy that has the greatest therapeutic impact on cancers while posing minimal side effects and toxicity is required.

Our patient required no further treatment for carcinoid post-surgery but was put on R-CHOP regimen for management of DLBCL. He has till now has completed 6 cycles of chemotherapy, and is doing fine, similar to observed in all the other 3 cases reported earlier, wherein they have been followed up for upto a year or more. [5,11-12]

The aetiology of the increased risk of another primary malignancy in patients with a carcinoid tumor remains unclear. Zucker et al. proposed that malignant diathesis of carcinoids may be a result of secretion of biologically active compounds by neuroendocrine cells. These regulatory peptides, which are found mostly in gut and brain, function as gastrointestinal hormones and neurotransmitters. There is evidence that many of that many of the secreted peptides have growth factor properties, and that non carcinoid tumor cells can overexpress receptors for these regulatory peptides. Carcinoid tumors also produce non-endocrine peptides that may play a role in carcinogenesis. For instance, transforming growth factors are elaborated in gut and bind to specific high-affinity receptors on fibroblasts or endothelial cells. Their principal role is to regulate cell growth and differentiation, including angiogenesis and blood vessel ingrowth in tumors. PDGF, EGF, TGF, insulin-like growth factors may play a central role in genesis of SPM in patients with carcinoid tumors [13,14].

Studies in the past have also stated that a relationship between NETs and lymphoreticular tumours does exist, as they both share some signalling molecules and receptors, indicating that neuroendocrine hormones may have an impact on the proliferation and mitogenesis of lymphoid cells and diseases might develop as a result of changes in this pathway [15].

CONCLUSION

Synchronous lymphoreticular tumor of the gastrointestinal tract and carcinoid tumours are rare malignancies. Our article presents an uncommon association between an appendiceal carcinoid tumor and ileal diffuse large B cell lymphoma, underscoring the need of both immunohistochemical and histological staining in the diagnosis and the role of surgery in treatment. Moreover, enhancing comprehension of the interplay between carcinoid and lymphoma in the context of synchronous/collision tumors could lead to better patient care and outcomes.

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