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Case Report

Metachronous triple primary malignancies of duodenum, skin, and appendix in the absence of common hereditary syndromes: a case report

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Abstract: Multiple primary malignancies (MPMs) are a more severe and common problem to exist in the field of clinical Oncologist. The case of a 61-year-old male with three metachronous primary cancers over a span of 36 months: duodenal mucinous adenocarcinoma, facial basal cell carcinoma, and appendiceal goblet cell adenocarcinoma. In 2021 the patient initially visited the hospital with clinical features consistent with acute cholangitis, which was later determined through a comprehensive series of examinations, such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic biopsy, to be a duodenal adenocarcinoma, thus undergoing pancreaticoduodenectomy followed by adjuvant FOLFOX (folinic acid + fluorouracil + oxaliplatin) chemotherapy. Subsequently, a facial basal cell carcinoma was excised in 2022, and an appendiceal goblet cell adenocarcinoma was discovered by chance during appendectomy for a suspected abscess in 2023, so further FOLFOX chemotherapy was administered. Duodenal tumor showed mismatch repair (MMR) proficiency and wild-type p53 by immunohistochemistry but germline testing was not performed. This case shows that MPM can imitate common benign diseases, need to do a thorough investigation, highly vigilant. To establish criteria of clinicopathological stringency, and showed that the possible defining characteristic in the absence of any specific inherited syndromes was probably chronic inflammation which acted as "common soil". Radical surgery and one consistent chemotherapeutic regimen for two adenocarcinomas, a practical route. Finally, it's stated in this report here that comprehensive long-term multimodality follow up in all the cancer survivors should be done to get the early new primary malignancies.

Keywords: Multiple primary neoplasms, duodenal neoplasms, appendiceal neoplasms, adenocarcinoma, basal cell carcinoma

Introduction

Diagnosis and treatment of multiple primary malignant neoplasms (MPM) diagnoses occur in a patient having two or more-site distinctly different cancers and the prevalence of more difficult events presenting to oncology clinics [1]. Although there have been improvements in cancer screening and survivorship, the increased incidence of MPMs has not occurred in sequence, with a reported prevalence of 0.7%-11.7% [2, 3]. The occurrence of three or more different primary cancers is even more rare, and there are even greater difficulties in terms of the cause of the disease, the best treatment sequence, and long-term follow-up.

The pathogenesis of MPMs is complex and multiple factors are often combined to be the cause of MPMs, such as genetic factors, environmental exposure factors, lifestyle factors, etc., and may also include the late effects of the previous treatment of oncology [2, 4-6]. An important foundation of the workup is excluding known hereditary cancer syndromes, including but not limited to Lynch syndrome, Li-Fraumeni syndrome, which are associated with various malignancies due to germline mutations [7, 8]. But a lot of MPMs happen without a clearly inherited syndrome. This resulted in the "common soil" or "field cancerization" hypothesis suggesting that there is a shared predisposition, such as a chronic inflammatory micro-

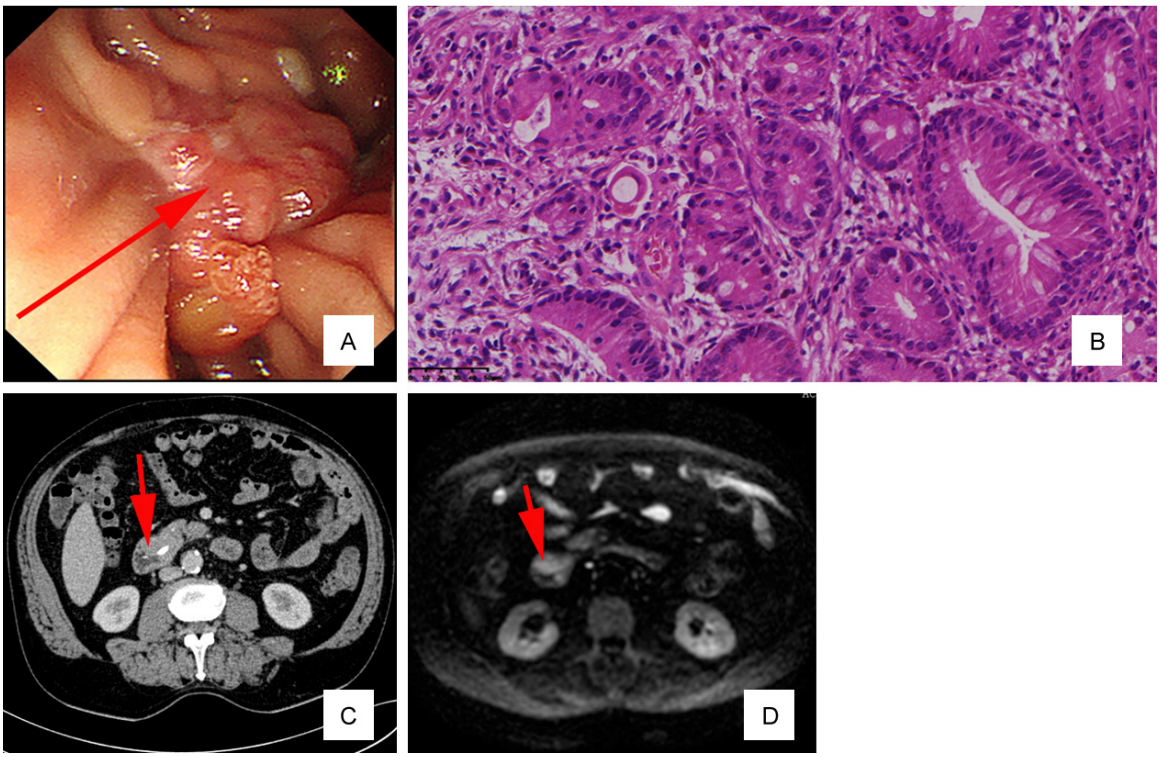

Figure 1. Diagnostic workup for the duodenal lesion. A. ERCP image revealing a cauliflower-like mass at the duodenal papilla (red arrow). B. Photomicrograph of the papillary biopsy showing architectural distortion and cytological atypia, diagnostic of high-grade intraepithelial neoplasia (H&E stain). C. Contrast-enhanced abdominal CT demonstrating an enlarged duodenal papilla (red arrow). D. Abdominal MRI (DWI sequence) showing a mass at the duodenal papilla with restricted diffusion (red arrow), highly suspicious for malignancy. Scale bar = 50 μm, original magnification: 400×.

environment or an immunologically compromised state, which allows for the independent development of tumors in different tissues [9, 10]. Clinically, MPMs bring great difficulties to clinical diagnosis as new symptoms are prone to be mistaken as the symptoms of the original cancer or a common benign disease, thus causing the diagnosis to be missed.

Case report on the rare occurrence of three metachronous primary malignancies in a 61-year-old male over a 3-year period including duodenal mucinous adenocarcinoma, facial Basal cell carcinoma, appendiceal goblet cell adenocarcinoma. The main purpose of this report is as follows: The first is to show the process of diagnosis, which reveals that the initial appearance is similar to a common surgical emergency; The second is to conduct a rigorous discussion based on criteria to support the determination of these three as the primary tumors; The last is to explore the possible role of chronic inflammation as a "common soil" in the absence of a classic hereditary syndrome, and to be aware of the shortcomings of immunohistochemical screening alone. In addition, we state the reasons for the consistent treatment strategy, and illustrate the application of a fixed chemotherapy protocol for two distinct gastrointestinal adenocarcinomas. This emphasizes more continuous clinical care after multiple oncoplastic therapies and more applicable pathological learnings.

Case presentation

In February 2021, a 61-year-old male presented to the emergency department with a 4-day history of periumbilical pain and a 1-day history of fever. Leukocytosis (white blood cell count 11.25 × 10^3/L), hyperbilirubinemia (total bilirubin 52.5 μmol/L, direct bilirubin 32.5 μmol/L), elevated liver enzymes (ALT 110 U/L, GGT 955 U/L), and markedly elevated high-sensitivity C-reactive protein (132.76 mg/L) suggested cholestatic liver damage. Abdominal CT showed cholelithiasis, a stone in the lower part of the common bile duct, dilation of the biliary

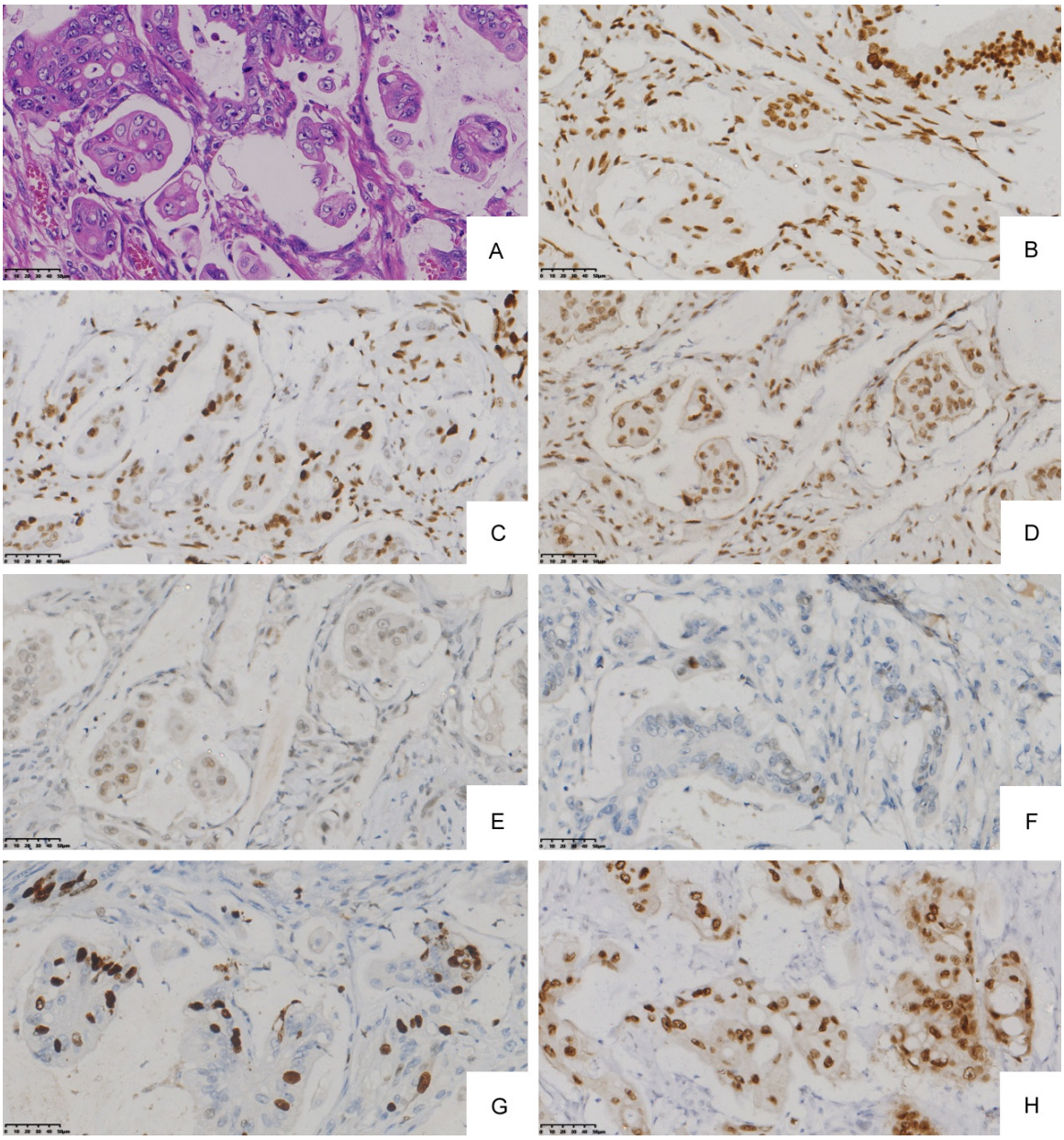

Figure 2. Postoperative pathological analysis of the pancreaticoduodenectomy specimen. (A) Photomicrograph showing moderately differentiated mucinous adenocarcinoma invading the deep muscular layer (H&E stain). (B-H) Immunohistochemical staining reveals intact nuclear expression of mismatch repair proteins: (B) MSH2, (C) MSH6, (D) MLH1, and (E) PMS2. (F) Wild-type p53 expression pattern. (G) High Ki-67 proliferative index (approximately 70%). (H) Nuclear positivity for CDX-2, confirming intestinal differentiation. Scale bar = 50 μm, original magnification: 400×.

tree, and inflammatory changes in the pancreas and peri-gastric area. An ERCP conducted in a patient displaying a cauliflower-like mass at the duodenal papilla was done (**Figure 1A**). High grade intraepithelial neoplasia was found in the biopsy of the lesion (**Figure 1B**). An enlarged duodenal papilla with limited diffusion was found to be a subsequent contrast enhanced CT and MRI image, strongly suggesting cancer (**Figure 1C** and **1D**). On March 2, 2021, the patient had a pancreaticoduodenectomy. A moderately differentiated mucinous adenocarcinoma of the duodenum (4.0 × 3.5 × 2.0 cm), which invaded into the deep muscular layer and spread to two out of the ten peripancreatic lymph nodes (pT2N1M0) was confirmed by the final pathology (**Figure 2A**). Immunohistochemistry (IHC) indicated a Ki-67

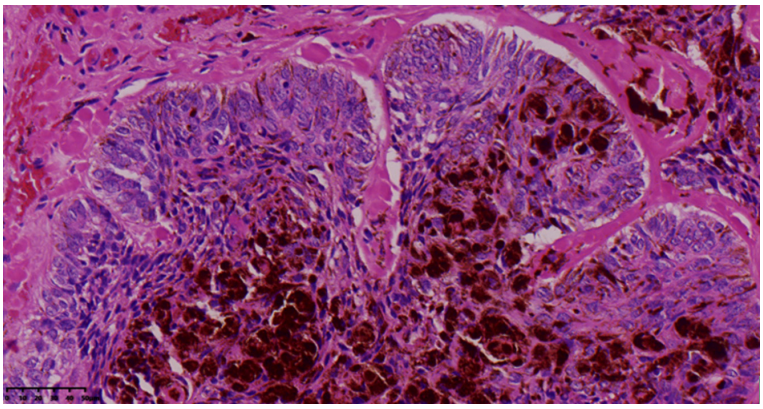

Figure 3. Postoperative histopathology of the facial lesion. Photomicrograph shows nests of basaloid cells with peripheral palisading, consistent with basal cell carcinoma (H&E stain). The surgical margins were free of tumor. Scale bar = 50 μm, original magnification: 400×.

proliferation index of 70%, wild-type P53, and competent mismatch repair protein levels (**Figure 2B-H**) (MSH2, MSH6, MLH1, PMS2 all positive). After 8 times of the Adjuvant FOLFOX postoperative treatment, the patient's symptom gone.

In the January 2022 routine follow up a skin lesion noted on the face and this was excised. The pathological test showed a basal cell carcinoma with clear surgical boundaries (pT1N0M0) (**Figure 3**).

After more than three months of conservative treatment for an appendiceal abscess, the patient was readmitted in December 2023. Follow-up abdominal CT scan showed remaining appendiceal thickening (**Figure 4A**). Laparoscopic appendectomy on 21 December 2023. Histopathological analysis unexpectedly showed an appendiceal goblet cell adenocarcinoma infiltrating the serosa (pT3N0M0) (**Figure 4B**). IHC confirmed diagnosis showing positive wild-type p53, ki-67 at 20%, ae1/ae3, ck20, cd56 (partial), cgA (focal), syn (partial), muc2 (**Figure 5**). Adjuvant chemotherapy was given to the patient with the FOLFOX regimen following a multidisciplinary meeting.

Discussion

This is the case that had remarkable three primary metastatic cancers of duodenal adenocarcinoma, basal cell carcinoma, and appendiceal goblet cell adenocarcinoma in 36-month time. In the clinic and manage the process of this patient, there are a few lessons to be learned about MPMs such as the diagnosis's difficulties, cause thoughts and treatment consistencies. It is instructive in this instance of a cancer arising from tissues of different embryonic origin (endoderm and ectoderm) in a patient without any heritable marker that is identified by IHC.

Criteria supporting classification as three independent primary malignancies

Regarding MPMs reporting we need the rules firm, when and how and when we say this is a tumor with independent first order, in which we don't call this a metastasis [11, 12]. Here we have used established clinicopathological criteria to support such a classification. First of all, the three tumors were quite different histologically: A moderately differentiated mucinous adenocarcinoma of the duodenum, a basal cell carcinoma of the skin, and a goblet cell adenocarcinoma of the appendix - this last confirmed by IHC to be a mixed tumor of both neuroendocrine and glandular elements. Secondly, they occurred in different organs (duodenum, facial skin, appendix) that had no anatomic proximity or a plausible pattern of metastasis. Thirdly, their presentation was metachronous, occurring sequentially over a 36-month period and disease-free intervals were present between diagnosis and treatment. And then every tumor was completely removed and histopathological showed characteristics suggestive of primary tumor at each site, the appendiceal tumor presented with primary growth pattern and no evidence of serosal deposit from elsewhere. Although we did not carry out comparative molecular profiling (such as whole-exome sequencing) to definitively rule out a clonal relationship - an extension of the future - these clinicopathological criteria together provided sufficient grounds to classify them as three separate primaries.

Diagnostic pitfalls and the "common soil" hypothesis

In the early diagnosis, a common phenomenon of oncology reoccurs: common symptoms can conceal some rare but dangerous diseases.

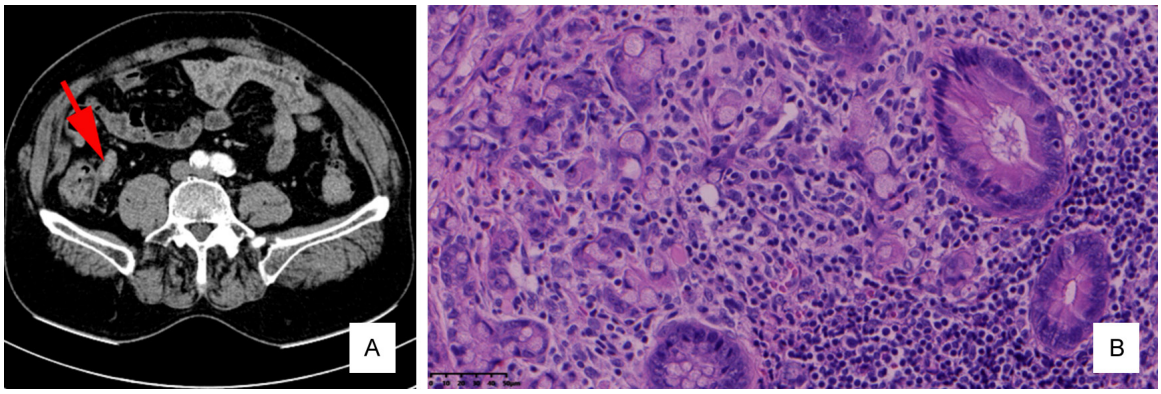

Figure 4. Appendiceal imaging and pathology. A. Follow-up contrast-enhanced abdominal CT shows a thickened appendix (red arrow) with surrounding inflammatory changes and abscess formation, which had improved compared to a scan from three months prior. B. Photomicrograph of the appendectomy specimen reveals goblet cell adenocarcinoma infiltrating through the muscularis propria into the subserosal tissue (H&E stain). Scale bar = 50 μm, original magnification: 400×.

Given the presentation of Charcot's triad, simple choledocholithiasis and acute cholangitis was very much likely [13]. But for this the peripancreatic infiltration as well as, more importantly, the ERCP which made way for a direct view of a cauliflower like duodenal papilla were critical. This pattern of an inflammatory process that hides a malignancy was also later heard in this patient's course. The case of appendiceal goblet cell adenocarcinoma first appears to be an appendiceal abscess and then it is diagnosed as appendiceal abscess after surgical treatment and histopathological examination. This is in line with the literature which states that in elderly patients with biliary obstruction, the existence of gallstones should not be used as grounds to give up the investigation for an occult malignancy, as the two may coexist or the stones may be a secondary result of the tumor [14]. In appendicitis context, for instance, if it is complicated or an elderly person, there can be an underlying appendiceal neoplasm [15].

The cause of such a rapid occurrence of three different cancers requires careful consideration. Our first guess was an inherited cancer syndrome. There is full expression of mismatch repair protein and the normal pattern of P53 gene in the duodenal carcinoma, IHC alone can rule out Lynch and Li-Fraumeni syndromes [16, 17]. A huge problem to point out IHC is a screening not a genetic test. Because of no germline genetic sequencing in this case means that hereditary syndromes due to mutation on gene not being assessed through IHC (e.g. MUTYH, BRCA1/2, ATM) or low penetrance alleles cannot be formally ruled out. This is an important study limitation and a significant factor for subsequent management consideration. Without evidence for a classic genetic syndrome from the available tests, the "common soil" hypothesis provides a good framework [9]. And had quite a bit of long-standing chronic inflammation, like he had cholelithiasis and cholecystitis and a long-standing appendiceal abscess. Chronic inflammation is well recognized as a carcinogen at different organs, creating a protumor environment by creating reactive oxygen species, promoting cell division and triggering genetic mutation [18]. This shared "inflammatory soil" may have provided a permissive background for carcinogenesis in the duodenum and appendix. And also, the step-by-step development of cancers makes one think of maybe there is a messed up immune surveillance system that couldn't catch the bad guys when they first popped up in different tissues [19].

Clinical lessons and therapeutic coherence

This case offers several specific and actionable insights to clinicians. First, it emphasizes that a high degree of suspicion should be maintained in the face of common clinical presentations such as acute cholangitis or appendicitis in the middle-aged and elderly population, as they may be the first manifestation of an underlying malignancy. This experience recon-

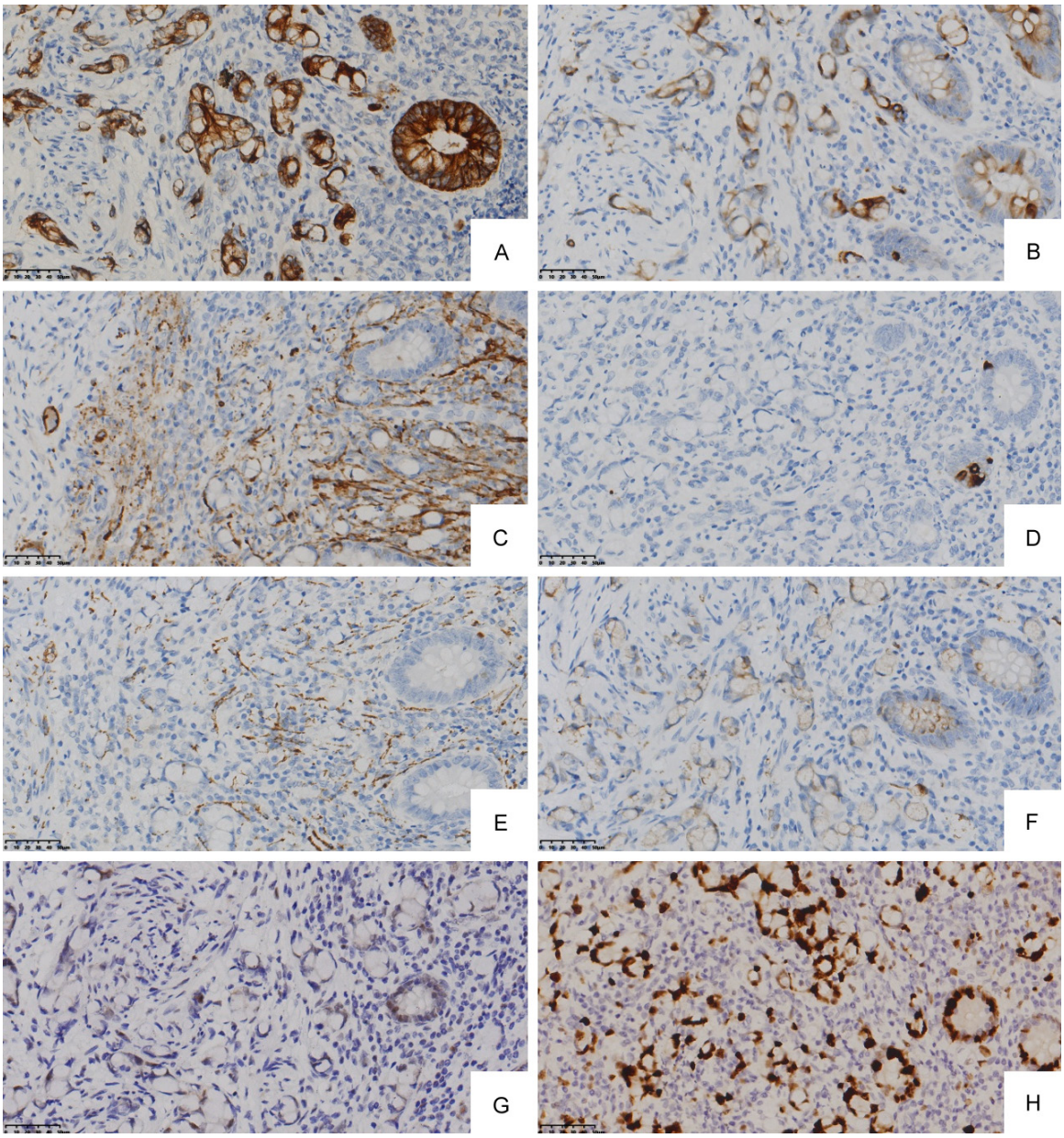

Figure 5. Immunohistochemical profile of the appendiceal goblet cell adenocarcinoma. The tumor cells are positive for (A) AE1/AE3, (B) CK20, (C) CD56 (partial), (D) CgA (focal), (E) Syn (partial), and (F) MUC2. (G) Wild-type p53 expression pattern is observed. (H) The Ki-67 proliferative index is approximately 20%. Scale bar = 50 μm, original magnification: 400×.

firms the indescribable diagnostic value of direct endoscopy with biopsy in patients with obstructive jaundice, and this article also argues for the conclusion and therapy of the case of appendicitis, even at the cost of long-term conservative therapy in cases that are more complicated and permanent.

Furthermore, the case can also reflect how to deal with the problem of diagnostic uncertainty when there is clinical suspicion of a hereditary syndrome but immunohistochemical screening fails to show positive results; in the gray area of these, clinicians need to consider both the possibility of undetected genetic factors and alternative systemic causes such as chronic inflammation. From a therapeutic point of view, the two metastatic gastrointestinal adenocarcinomas were successfully treated with the FOLFOX regimen repeatedly and tolerable, and

a pragmatic and coherent strategy was achieved [20, 21]. Although this was extrapolated from data in histologically similar cancers and there is limited evidence for certain components of the tumor, its application here, as guided by the patient's previous ability to tolerate it and the clinical course, provides a practical model of how to apply a chemotherapeutic algorithm in a standardized yet flexible way to multiple primary malignancies.

Finally, it makes a valid case that we have to change our healthcare for those that we have beaten cancer for life. It needs a model of total multi-organ watch which goes past keeping watch for a recurrence of the initial most cancers and holds high a great deal of doubt about new primaries. Occurrence of three big malignancies in three different parts of the body within a short time is also a proof of this way.

Conclusion

And then a rather chaotic example of metachronous primary malignancies will draw some out for you that will be the most relevant in a clinical sense. Firstly, it is necessary to pay attention to the fact that one should not be limited to the common preliminary diagnosis in the diagnosis of elderly patients, and the appearance of acute cholangitis is actually a case of duodenal carcinoma. Secondly, we can make a rigorous argument that they should all be considered three separate primary tumors, in line with the criteria for histology, anatomy and timing. Thirdly, IHC screening failed to support the classic hereditary syndromes, no germline sequencing was done and thus a role of undetected genetic elements cannot be excluded. The sequence of occurrence of the three different kinds of cancer without IHC evidence of classic hereditary syndromes strongly indicates a "common soil" predisposition and the possibility of chronic inflammation as a unifying etiological factor although lack of germline sequencing is recognized. Fourthly, it reaffirms that the diagnostic process for appendiceal goblet cell adenocarcinoma must be through a definitive pathologic study, although apparently a conservative management works successfully.

From a therapeutic perspective, the integration of radical surgery and the FOLFOX regimen for two different gastrointestinal adenocarcinomas in the treatment of two MPMs, one of which being rare, proves that even radical treatments involving combined radical surgery and the FOLFOX regimen can achieve good results when applied in two diseases and one rare case; Finally, it will serve as a lesson to clinicians to keep a higher suspicion for new primary malignancies in patients with a cancer history and call for continuous, all-round and long-term follow-up to discover and handle potential new malignancies at an early stage. The special clinical sequence in this report is manifested in the form of these values.

Disclosure of conflict of interest

None.

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