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Inflammatory Fibroid Polyps and Platelet-Derived Growth Factor Receptor Mutation Analysis

İnflamatuvar Fibroid Polipler ve Platelet Türevli Büyüme Faktörü Reseptör Mutasyon Analizi

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ÖZ

Amaç: İnflamatuvar fibroid polip gastrointestinal trakta çok nadir görülen tümörlerden biridir. Klinik olarak çok farklı bulgulara neden olabileceği için tanı zorluğuna neden olur. Ayrıca, histopatolojik olarak da malign bir lezyonu taklit edebilir. İnflamatuvar fibroid poliplerde platelet türevli büyüme faktörü reseptör (PDGFR) α mutasyon varlığı ile ilgili olarak bilgilerimiz artmaktadır.

Olgular: Burada ikisi ince barsakta, biri midede lokalize olan üç farklı tümörün histopatolojik ve immünohistokimyasal bulguları inflamatuar fibroid polip ile uyumlu olarak yorumlandı. Her iki olguda da PDGFR mutasyon analizi yapıldı ve mutasyon varlığı saptandı.

Sonuç: İnflamatuvar poliplerin patogenezi ve histogenezi belirsizdir. Hem iyi huylu hem de kötü huylu tümörleri taklit eden bu tümörlerde PFGR mutasyonlarının varlığını destekleyen sonuçlar elde ettik**.**

Anahtar sözcükler: İnflamatuvar fibroid polip; *PDGFRA* mutasyonu; gastrointestinal trakt

ABSTRACT

Aim: Inflammatory fibroid polyp is one of the most rarely seen tumors in the gastrointestinal tract. It is clinically confusing as it can cause many different findings. On the other hand, it may histopathologically mimic a malignant lesion. Our knowledge about the presence of platelet-derived growth factor receptor α *(PDGFRA)* mutation in inflammatory fibroid polyps are increasing.

Cases: Herein, histopathological and immunohistochemical findings of three different tumors, two localized in the small intestine and one in the stomach, were interpreted as compatible with inflammatory fibroid polyp. PDGFR mutation analysis was performed in both cases and the presence of mutation was detected.

Conclusion: The pathogenesis and histogenesis of inflammatory fibroid polyps are uncertain. We obtained results supporting the presence of PFGR mutations in IFPs mimicking both benign and malignant tumors.

Keywords: Inflammatory fibroid polyp; *PDGFRA* mutation; gastrointestinal tract

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Introduction

Inflammatory fibroid polyp (IFP) is one of the rarely seen localized benign lesions of the gastrointestinal tract. They are usually located in the submucosa and often develop into a luminal polypoid shape (1). IFP was firstly described by Vanek as submucosal granuloma containing eosinophilic infltration (2). Afterwards, a number of different nomenclatures have been made that reflect more frequently its microscopic appearance together with different interpretations such as eosinophilic granuloma, gastric fibroma containing eosinophilic infiltration, and inflammatory pseudotumor. More often used and accepted terminology for these lesions is the term "inflammatory fibroid polyp" coined by Helwig and Rainer (3). They can be clinically confusing as they can cause different clinical symptoms (4). In addition they can confused with malignant lesions, histopathologically (5, 6).

The pathogenesis and histogenesis of IFPs are uncertain. For a long time, it was considered reactive in nature (autoimmune, allergic). Presence of overexpression and mutations in platelet-derived growth factor receptor α *(PDGFRA)* has led to considering inflammatory fibroid polyp a neoplastic process (7, 8). Today it is considered as a true neoplasm. PDGFRA is a receptor tyrosine kinase and composed of combinations of A and B isoforms (AA, AB, BB). It is produced and secreted by megakaryocytes, activated vascular endothelial cells, macrophages, fibroblasts, smooth muscle cells. PDGFRA is activated by mutations in 55% to 70% of inflammatory fibroid polyps.

The aim of the study is to emphasize awareness of the presence of such lesions, which can cause clinically different findings and mimic many benign or malignant lesions histopathologically. Also, it is to support the presence of PGFR mutation association with these lesions.

Materials and Methods

This study covers three different cases diagnosed between 2013 and 2018. One case was sent as a ready-made paraffin block from the outer center as a consultation. All cases were examined histopathologically, immunohistochemical staining required for differential diagnosis. In addition, PDGFRA mutation analysis was performed in the first two cases. Isolation could not be made from the tissue sample of the last case. A molecular genetic analysis for *PDGFRA* (exons 12, 14 and 18) genes was performed, in paraffin micro dissection specimens, by the PCR-direct sequencing method (GeXP Genetic Analysis System, Beckman Coulter, Brea, CA, USA), as previously described (9).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Case 1. A 65 -year- old female patient underwent endoscopic submucosal dissection (ESD) with an initial diagnosis of gastric polyp (Figure 1 a, b, c). The specimens obtained had morphological features consisting of spindle cells with a slightly myxoid background that advanced from submucosa into lamina propria (Figure 1d). Prominent eosinophil leukocytes and vascular structures with concentric fibrosis around some of them were noted. There was no atypia and mitosis. Immunohistochemically CD34 (CD34; My10; 1:200; BD, Franklin Lakes, NJ, USA)- positive, mildly and focally positive smooth muscle actin (SMA; 1A4; 1:200; DAKO), and also CD117 (Polyclonal; 1:600; DAKO), DOG-1 (DOG1; K9; 1:50; Leica Biosystems,Nussloch,Germany), anaplastic lymphoma kinase (ALK; D5F3; Prediluted; Roche Diagnostics GmbH), S-100 (Polyclonal; 1:800; Leica Biosystems) and desmin (DE-R-11; 1:100; Leica Biosystems) -negative spindle cells were detected.

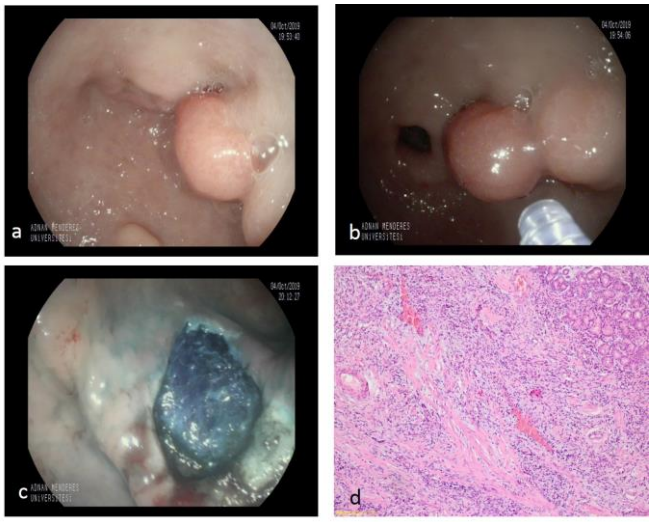

Figure 1. Endoscopic images: a) The appearance of the polyp endoscopically before the procedure, b) The appearance of the polyp after submucosal solution injection, c) The polyp base after endoscopic submucosal dissection, d) Granulation tissue-like findings consisting inflammatory cells in the submucosa and lamina propria (H&E x100).

Case 2. Blocks of surgical specimens of small intestine belonging to a 53-year-old female patient sent for consultation where differential diagnosis between inflammatory myofibroblastic tumor and gastrointestinal stromal tumor (GIST) could not be made were examined. Microscopic examination revealed ulcerated surface, edematous-loosened background containing various vascular structures of varying thickness, granulation tissue-like findings consisting of mixed types of inflammatory cells very rich in eosinophil leukocytes together with spindle, and patchy areas of seemingly epitheloid cells (Figure 2a).

In the perivascular distance, the cuff-shaped lymphoid cells and the concentric arrangement of the spindle cells were noted. Immunohistochemically CD34- positive; CD117, DOG-1, ALK, S-100, smooth muscle actin and desmin-negative spindle cells were detected (Figure 2b).

Case 3. The third case was a 78-year-old male patient who underwent partial ileum resection for strangulated hernia. Macroscopic evaluation revealed an ulcerated lesion on the surface away from both surgical margins.

Microscopically, morphological appearance characterized with spindle cells, small to medium-sized vascular structures and submucosal infiltration rich in inflammatory cells mostly consisting of eosinophil leucocytes was observed (Figure 2c). Concentric arrangement of spindle cells around the vessels was noted. Atypia, necrosis and mitosis were not observed. Immunohistochemically CD34- positive; CD117, DOG-1, ALK, S-100, smooth muscle actin and desmin-negative spindle cells were detected (Figure 2d). Ki-67 proliferation index was low (1-2%) in all three cases.

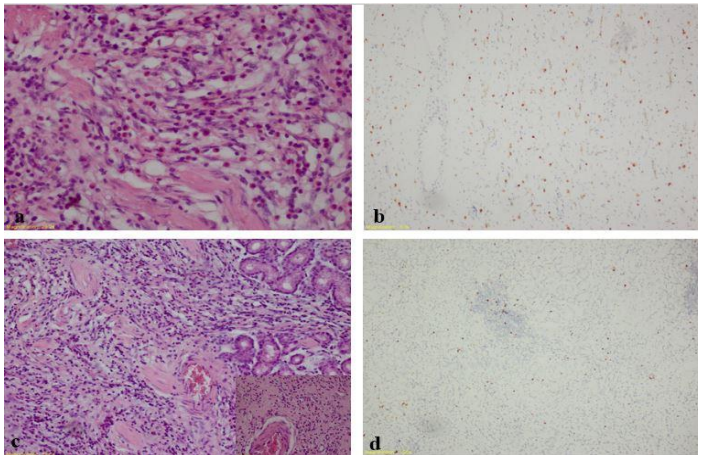

Figure 2. Histological images: a) Mixed types of inflammatory cells very rich in eosinophil leukocytes in the edematous-loosened background (H&E x200), b) Immunohistochemically spindle cells negative with CD117 (mast cells stained positive with internal control), c) Morphological appearance characterized with small to medium-sized vascular structures and submucosal infiltration rich in inflammatory cells mostly consisting of eosinophil leucocytes (small box: Concentric arrangement of spindle cells around the vessels) (H&E x200), d) Ki-67 proliferation index is too low.

Based on available histological and immunohistochemical findings the cases were interpreted as “Inflammatory Fibroid Polyp”. In addition, we evaluated the *PDGFRA* gene status. A molecular genetic analysis for KIT (exons 9, 11, 13 and 17) and PDGFRA (exons 12 and 18) genes was performed, in paraffin micro dissection specimens, by the PCR-direct sequencing method (GeXP Genetic Analysis System (Beckman Coulter, USA). We found mutations in this gene in the first two cases (Figure 3).

Discussion

IFPs can cause many different clinical symptoms such as gastrointestinal bleeding, abdominal pain, and vomiting depending on their size and localization (10). They may even mimic acute appendicitis. Sometimes they are asymptomatic and detected incidentally during endoscopic procedures performed for other indications. Thus they can be encountered with clinically different and confusing presentations. In addition they can create difficulties in differential diagnosis among histopathologically reactive processes, as well as many lesions containing benign or malignant spindle cell components (11).

The proliferation of spindle, stellat or epithelioid mesenchymal cells in the loose-edematous stroma rich in lymphocytes, eosinophils and mast cells is the typical morphological appearance of IFP. Stroma contains collagen fibers and is markedly vascularized. This vascularization is characterized by a striking ‘onion skin’ arrangement around the thin-walled blood vessels of the spindle cells. It is the responsibility of us, pathologists, to ensure the correct management of the patient by accurately identifying this confusing entity, both clinically and pathologically.

Although the presence of *PDGFRA* mutation supports our diagnosis, it does not exclude the possibility of GIST. However, some notable points were valuable in reaching this diagnosis. The first finding is intense leukocyte infiltration which is a very unexpected appearance for GIST. The other finding is that epithelioid morphology is predominant in GIST lesions with *PDGFRA* mutation. Moreover, CD117 and DOG-1 are positive in most GIST lesions. In all our cases, immunohistochemically CD117 and DOG-1 were negative.

In the differentiation from eosinophilic gastroenteritis, in addition to the typical histological features described, the presence of a mass-occupying lesion is also very important. Because any mass lesion can not be found in cases with eosinophilic gastroenteritis. Spindle cell lesions such as inflammatory fibrosarcoma, spindle cell carcinoid and GIST are among the other entities that should be kept in mind. The distinction between GIST and IFP can sometimes be histologically difficult. Immunohistochemically, both lesions are CD34-positive. CD117 and / or DOG-1 positivity in GIST is helpful in differential diagnosis. However, the most fundamental criterion is histopathology.Therefore, when we encounter the morphological appearance described above, inflammatory fibroid polyp should be considered. PDGFR mutation has been reported in different tumors (such as epithelial, mesenchymal) (12). The mutation seen in the inflammatory myofibroblastic tumor, which is in the differential diagnosis morphologically, has been identified as *PDGFRB* (13).

In cases where macroscopic evaluation cannot be performed together with microscopic evaluation (such as examination of preparations and / or tissue blocks sent for consultation, and small biopsy specimens), it is important that the clinician informs the the pathologist that the mass is polypoid, and also the pathologist should be aware of the presence of such a lesion during microscopic evaluation.

The pathogenesis of IFPs is not completely clear. It was initially thought to be the result of an inflammatory response to submucosal granuloma. It has been often reported that this submucosal granuloma was associated with a stimulus such as trauma, tuberculosis, sarcoidosis, Crohn's disease, and *helicobacter pylori* (14). In conclusion, although its histogenesis is controversial, it is generally described as true neoplasms with *PDGFRA*

mutations and cases with *PDGFA* mutation are reported(15).

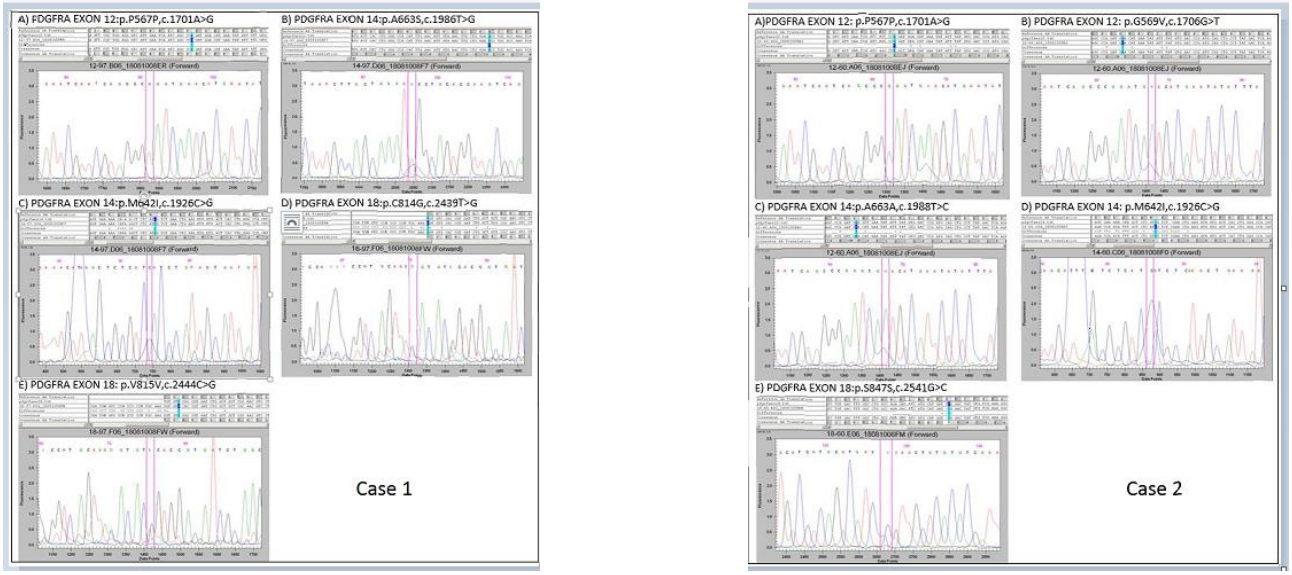

Figure 3. Results of *PDGFRA* mutation analysis for cases 1 and 2.

Conclusion

IFP is one of the most rarely seen tumors in the gastrointestinal tract. It should be kept in mind as a benign lesion that may cause different symptoms depending on its localization and size, which must be resected for treatment and may create difficulty in the differential diagnosis with low-grade spindle cell lesions from time to time. Recently, data on the presence of a *PDGFRA* mutation are accumulating. In our two cases, mutation was found in accordance with the literature. There is a need for accumulation of molecular knowledge about these rare and confusing lesions obtained in large-scale case series to be conducted in the future.

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