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Original Article

Inflammatory fibroid polyp: A series of 29 cases and a systematic review of the literature

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ABSTRACT

An inflammatory fibroid polyp (IFP) of the gastrointestinal tract is a localized, benign mesenchymal lesion consisting of spindle-shaped stromal cells, eosinophilic granulocytes, and some lymphocytes and plasma cells. The discovery of a frequent mutation of the platelet-derived growth factor receptor A (*PDGFRA*) gene was the first hint of a gene-regulating process in IFPs. The aim of this study was to investigate the interaction of inflammatory processes and the role of mutation and expression of the *PDGFRA* gene in the development of IFPs for the first time. We used immunohistochemistry to analyze the composition of inflammatory cells and next generation sequencing (NGS) to provide a broad overview of gene mutations.

We report on 29 cases of IFP. The mean age, gender differences, and localization were compatible with the literature. Spindle cell histomorphology was present in 79% of cases showing a typical onion skin-like perivascular arrangement and significantly high CD34 positivity ($p = 0.002$, Fisher's exact test). Eosinophilic granulocytes were present in an average density of 60 ± 49/high power field (HPF) (range: 15–200), and there was a significantly higher rate of IFPs larger than 2 cm in size ($p = 0.018$, Wilcoxon test). All but one cases could be analyzed by NGS. Mutations were observed in 17 cases (60.7%), including 13 (46.4%) mutations in the *PDGFRA* gene. Among the gastric lesions, mutations were found in exon 18 of the *PDGFRA* gene with amino acid exchange (Asp842Val) for eight out of 10 cases and in exon 12 in two cases. All three cases in the small intestine revealed mutation of the *PDGFRA* gene in exon 12. We found no *PDGFRA* mutation in our colonic cases. *PDGFRA* expression was significantly correlated with mutations of the same gene ($p = 0.005$, Fisher's exact test) and especially with mutations in exon 12 of the same gene ($p < 0.001$, Fisher's exact test). Interestingly, three of our cases (10.3%) without mutation or expression of the *PDGFRA* gene revealed an unusually high concentration of IgG-positive plasma cells (average: 140 ± 26/HPF, range: 110–160) and IgG4-positive plasma cells (average: 87 ± 21/HPF, range: 60–100). For comparison, an IgG4/IgG ratio of more than 0.4 is commonly observed in IgG4-related diseases. Our molecular results were in accordance with 113 genetically analyzed cases published to date. There was a correlation between the IFP site and mutation variants of the *PDGFRA* gene. IFPs were localized in the stomach in 49.1% of cases, in the small intestine in 47.3%, and in the colon in 3.6%. Exon 12 of the *PDGFRA* gene was mutated in 41.1% of cases and primarily occurred in the small intestine (82.6%). Exon 18 was mutated in 22.3% of cases and primarily occurred in the stomach (80.0%). The mutated codon interval 566–571 in exon 12 and codon 842 in exon 18 were compatible, as observed in a gastrointestinal stromal tumor. Conclusively, the correlation between mutation and expression of the *PDGFRA* gene points to different pathways in IFPs. Additionally, our data hint at a morphological but not genetic overlap between IFPs and IgG4-related pseudotumors.

1. Introduction

An inflammatory fibroid polyp (IFP) in a gastrointestinal tract (GIT) was first described in 1949 by Vanek [1]. It is a localized, benign neoplastic lesion. This type of polyp occurs mainly in middle-aged adults and most commonly in the stomach, where it represents about 0.1–3.0% of all polyps [2,3]. The majority of IFPs are asymptomatic and are discovered as an incidental finding during an endoscopy performed for

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unrelated reasons. The lesions are usually less than 3 cm in size and, when symptomatic, are usually associated with abdominal pain, weight loss, bleeding, dyspeptic symptoms, and iron deficiency anemia. Larger lesion can also lead to more important complications, such as obstruction, intussusception, and even hypovolemic shock [4–6].

Histologically, IFPs are typically polypoid and hypocellular lesions originating from the submucosa. The stroma is loose and edematous. The spindle-shaped and stellate cells typically express CD34 [7] and show a perivascular arrangement, described as "onion skin like." Additionally, the most characteristic histological feature is a scattered inflammatory infiltrate consisting mainly of eosinophiles and secondarily of lymphocytes, plasma cells, macrophages, and mastocytes [3]. Interestingly, IgG4-related pseudotumors (IgG4-RPT) with a ubiquitous appearance in all parenchymatous organs present a similar histological appearance consisting of spindle-shaped stromal cells infiltrated with scattered eosinophilic granulocytes. Thus, the ratio of IgG4/IgG cells is decisive for the diagnosis of IgG4-RPT.

The etiology of IFPs is currently unknown, although they were initially considered purely inflammatory lesions. The discovery of a frequent mutation of the platelet-derived growth factor receptor A (PDGFRA) gene was the first hint at a gene-regulated neoplastic process [8]. PDGFRA is located in chromosome 4q12 and involved in the stimulation of cellular growth signal pathways and cell differentiation [9]. The mutation has been found in 21.7% to 69.6% of IFPs, mostly occurring in exon 12 (more frequent in cases of small intestine onset with deletion/deletion-insertion) or exons 14 or 18 (typical of gastric forms, with the latter typical with D842V substitution) [3,8,10,11]. Interestingly, the same mutations in exons 12, 14, and 18 of the PDGFRA gene are also prevalent in up to 40% of gastrointestinal stromal tumors (GISTs) [12]. In contrast to GISTs with PDGFRA mutation, which are mainly epithelioid, the mesenchymal cells in IFPs are spindle shaped [13]. In this context, the role of PDGFRA mutation in diseases with eosinophilic granulocytes are a very remarkable phenomenon. An FIP1L1-PDGFRA fusion has also been described in idiopathic hypereosinophilic syndrome [14]. Although this fusion has not yet been found in IFPs, a possible link between increased eosinophilic granulocytes and PDGFRA has been found [15]. The rearrangement of PDGFRA plays a growing role in myeloid neoplasms with eosinophils [16]. Recently, mutation in exon 15 of the BRAF gene in PDGFRA wild type IFP, a gene with an established oncogenic role [17], has also been documented [18]. The aim of this study was to consider the significance of the expression and mutation of PDGFRA in IFPs for the first time and to determine how to differentiate them from other gastrointestinal lesions with stromal cell proliferation in association with eosinophilic granulocytes.

2. Material and methods

2.1. Study cases

IFP cases were selected from the archive of the Department of Pathology of the Medical University of Augsburg from the period of 2004 to 2021. The diagnosis was reevaluated by two experienced pathologists (BM and LF) according to the criteria of the World Health Organization classification [3]. Use of the tissue was approved by the local ethics committee in Munich (Reference number 21–1191).

2.2. Methods

2.2.1. Immunohistochemistry

We used the following panel of immunohistochemical antibodies: IgG, IgG4, CD34, and PDGFRA (Supplement Tab. 1). All reactions were developed using the Ventana Benchmark Ultra system, and the reactions were performed using the Ventana Ultravision detection system (Roche Diagnostics, Mannheim, Germany). The high-power field (HPF) referred to an area of 0.31 mm^2.

2.2.2. Molecular pathology

For next generation sequencing (NGS) analysis, tumor areas were fixed with formalin, embedded with paraffin, and marked on an hematoxylin & eosin-stained slide. Corresponding tissue areas were microdissected from subsequent unstained slides. Extraction of genomic DNA was performed by proteinase K digestion and fully automated purification using the Maxwell RSC FFPE Plus DNA Kit (AS1720; Promega, Madison, WI, USA) on a Maxwell CSC system (RUO mode; Promega). The DNA concentration was measured fluorometrically using a QuantiFluor ONE dsDNA System (Promega).

2.2.2.1. Library preparation and sequency by synthesis sequencing. For this study, the multiplex Polymerase Chain Reaction-based AmpliSeq Cancer HotSpot Panel V2 (Illumina Technologies, San Diego, CA, USA) was used. The panel consists of 207 primer pairs for the detection of hotspot mutations in 50 cancer-related genes. Amplicon library preparation was performed using approximately 10 to 100 ng of DNA, as recommended by the manufacturer. In brief, the DNA was mixed with a primer pool containing all primers for generating the amplicons and with the AmpliSeq HiFi master mix. The master mix was transferred to a PCR cycler. PCR cycling conditions were initially denatured at 99 °C for 2 min, followed by 21 cycles first at 99 °C for 15 s and then at 60 °C for 4 min. After the PCR reaction, primer end sequences were partially digested using the FuPa reagent according to the manufacturer's instructions; this step was followed by the ligation of barcoded sequencing adapters (AmpliSeq CD Indexes Set A; Illumina Technologies). The final library was purified using AMPure XP magnetic beads (BeckmanCoulter, Krefeld, Germany) and was quantified using the QuantiFluor ONE dsDNA System (Promega). The individual libraries were diluted to a final concentration of 9 pmol/L, and 16 libraries were pooled and processed for sequencing by synthesis using a MiSeq reagent kit V2 (300cycles) on a MiSeq System (Illumina Technologies).

A secondary analysis was performed using the application Generate FASTQ (Version 2.0.01.17, RUO; Promega) and DNA Amplicon (Version 2.1.0.19, RUO; Promega) on the Local Run Manager (Version 1.0.0.7; Illumina Technologies). The reads were aligned to the human reference sequence build hg19. Detection of single nucleotide variants and indel polymorphisms, relative to the human reference sequence, was performed using the BaseSpace Variant Interpreter (Illumina Technologies).

2.2.2.2. Statistical analysis. For statistical analysis, a two-sample Wilcoxon tests and Fisher's exact tests were computed using the software R, version 4.1.2 (R Core Team, Vienna, Austria 2021). P values of less than 0.05 were considered significant.

3. Results

In the period from 2004 to 2021, 29 cases of IFP representing routine surgical specimens were diagnosed (Table 1). The mean age of diagnosis was 61 ± 14 years (range: 31–91). Female patients represented 62% of cases, and male patients represented 38%. IFP was located in the stomach in 58.6% of cases, in the colon in 24.1%, in the small intestine in 10.3%, and in the esophagus in 6.9%. The macroscopic appearance was polypoid with an average size of 1.8 ± 1.3 cm (range: 0.4–5.5 cm). The highest average size was observed in the small intestine at 3.2 cm, followed by the esophagus at 1.7 cm, stomach at 1.7 cm, and colon at 1.3 cm. Additional immune diseases were observed in 14% of patients and malignancies in 28%. However, no correlation was found with any clinico-pathological or immunohistochemical parameters or mutations.

Histological examination consistently showed loose stroma out of spindle cells, partly with discrete inflammatory cells. In 79% of cases, the spindle cells were arranged in a typical concentric, onion skin-like perivascular pattern and disclosed significant CD34 positivity ($p = 0.002$, Fisher's exact test) (Fig. 1; Table 1). Interestingly, a significantly higher concentration of CD34-positive cells ($p = 0.014$, Fisher's exact

Table 1
Clinicopathological and immunohistological data of own cases (-, *absent; +, weak; ++, moderate; +++, strong).*

Case Nr.	Age (year)	Gender	Organ	Size (cm)	Onion-skin-pattern	CD34	Eosinophils/ HPF	IgG/ HPF	IgG4/ HPF	IgG4/ IgG	PDGFRA expression	Next generation sequencing	Additional autoimmune disease	Additional neoplastic lesion
1	50	M	esophagus	2,5	yes	+++	100	160	110	69%	positiv	not done; insufficient DNA quality	none	none
2	45	M	esophagus	0,8	yes	+	50	60	15	25%	negativ	**BRAF** (NM_004333.4); Exon 15; c.1799 T>A; p. Val600Glu (COSM476); VAF 9; 144/ 1692 (Q100)	none	none
3	73	F	stomach	1,2	no	–	20	110	80	73%	negativ	no pathology	myasthenia gravis	none
4	46	F	stomach	2	yes	+++	100	35	10	29%	negativ	no pathology	none	none
5	69	F	stomach	1	yes	+++	60	20	9	45%	negativ	**PDGFRA** (NM_006206.5); Exon 18; c.2525A>T; p.Asp842Val (COSM736); VAF 15; 158/1071 (Q100)	none	none
6	56	M	stomach	1	yes	+++	110	10	0	0%	positiv	**PDGFRA** (NM_006206.5); Exon 18; c.2525A>T; p.Asp842Val (COSM736); VAF 4; 46/1227 (Q100)	none	basal cell carcinoma (skin)
7	50	F	stomach	2	yes	+++	80	0	0	0%	negativ	**PDGFRA** (NM_006206.5); Exon 18; c.2525A>T; p.Asp842Val (COSM736); VAF 5; 39/817 (Q100)	none	none
8	74	F	stomach	3,5	yes	+++	80	30	10	33%	negativ	**PDGFRA**; (NM_006206.5); Exon 18; c.2526_2537Del p.I843_D846Del (COSM96892) (VAF 2, Q42)	none	none
9	58	M	stomach	1	no	–	20	12	3	25%	negativ	**TP53** (NM_000546.5); Exon 6; c.659A>G; p. Tyr220Cys (COSM10758); VAF 5; 50/994 (Q100)	none	early gastric cancer and adenocarcinoma (nose)
10	91	F	stomach	1	yes	+++	30	0	0	0%	negativ	no pathology	none	none
11	64	F	stomach	1	yes	+++	60	8	0	0%	negativ	**PDGFRA** (NM_006206.5); Exon 18; c.2525A>T; p.Asp842Val (COSM736); VAF 17; 107/617 (Q100)	none	none
12	67	F	stomach	1	yes	+++	20	16	1	6%	negativ	no pathology	none	gastric GIST
13	66	F	stomach	0,8	yes	+++	100	0	0	0%	negativ	no pathology	asthma	Adenocarcinoma (colon and stomach)
14	76	M	stomach	0,8	yes	+++	90	8	3	38%	negativ	no pathology	none	none
15	49	M	stomach	0,8	yes	+++	15	25	0	0%	negativ	**PDGFRA** (NM_006206.5); Exon 18; c.2525A>T; p.Asp842Val (COSM736); VAF 11; 79/722 (Q100)	none	none
16	49	F	stomach	4	yes	+++	180	0	0	0%	positiv	**PDGFRA** (NM_006206.5); Exon 12; c.1698_1712del; p.Ser566_Glu571delinsArg	none	acinar NSCLC

(*continued on next page*)

Table 1 (*continued*)

												(COSM12418); VAF 31; 331/1068 (Q100)		
17	56	M	stomach	1	yes	+++	150	5	1	20%	negativ	**PDGFRA** (NM_006206.5); Exon 18; c.2524_2525delinsCT; p.Asp842Leu; VAF 16; 137/872 (Q100)	none	none
18	68	F	stomach	2,5	yes	++	140	20	7	35%	positiv	**PDGFRA** (NM_006206.5); Exon 12; c.1682T>A; p.Val561Asp (COSM739); VAF 23; 133/581 (Q100) **PIK3CA** (NM_006218.3); Exon 21; c.3140A>G; p.His1047Arg (COSM775); VAF 17; 146/862 (Q100)	none	none
19	52	F	stomach	4,5	yes	+++	200	7	2	29%	negativ	**PDGFRA** (NM_006206.5); Exon 18; c.2525A>T; p.Asp842Val (COSM736); VAF 5; 21/392 (Q100) **KRAS** (NM_033360.3); Exon 2; c.35G>C; p.Gly12Ala (COSM522); VAF 19; 105/546 (Q100) **TP53** (NM_000546.5); Exon 5; c.524G>A; p.Arg175His (COSM10648); VAF 13; 63/514 (Q100) **APC** (NM_000038.5); Exon 16; c.4348C>T; p.Arg1450Ter (COSM13127); VAF 40; 76/189 (Q100)	none	none
20	50	F	small intestine	0,7	yes	+	20	23	8	35%	positiv	**PDGFRA** (NM_006206.5); Exon 12; c.1682T>A; p.Val561Asp (COSM739); VAF 15; 97/669 (Q100)	none	none
21	63	F	small intestine	5,5	yes	+	80	30	0	0%	positiv	**PDGFRA** (NM_006206.5); Exon 12; c.1698_1712del; p.Ser566_Glu571delinsArg (COSM12418); VAF 4; 28/718 (Q100)	sarcoidosis	none
22	83	F	small intestine	3,5	no	–	40	3	1	33%	positiv	**PDGFRA** (NM_006206.5); Exon 12; c.1698_1712del; p.Ser566_Glu571delinsArg (COSM12418); VAF 33; 202/619 (Q100)	none	none
23	66	M	colon	0,4	no	–	80	150	70	47%	negativ	no pathology	none	none
24	31	M	colon	1,4	yes	+	80	15	3	20%	negativ	no pathology	morbus Crohn	none
25	50	F	colon	1	no	–	30	19	3	16%	negativ	no pathology	none	none
26	46	F	colon	0,8	yes	+	20	15	4	27%	negativ	no pathology	none	invasiv ductal carcinoma (breast)
27	56	F	colon	1,2	yes	+++	20	5	2	40%	negativ	**PIK3CA** (NM_006218.3); Exon 21; c.3140A>G; p.His1047Arg (COSM775); VAF 11; 39/368 (Q100) **EGFR** (NM_005228.4); Exon 7; c.866C>A; p.Ala289Asp (COSM21685); VAF 17; 35/210 (Q100)	none	none
28	86	M	colon	3	yes	+++	50	11	4	36%	negativ	**KRAS** (NM_033360.3); Exon 3; c.183A>C; p.Gln61His	none	gastric adenocarcinoma

(*continued on next page*)

Table 1 (*continued*)

29	75	M	colon		1	no	–	60	0	0%	negativ	(COSM554); VAF 26; 367/1433 (Q100) no pathology	none	rectal adenocarcinoma

test) and lymphocytes ($p = 0.019$, Fisher's exact test) were observed in the upper tract than in the colon. Two gastric lesions hinted at epithelioid cytomorphology (Fig. 2-A,C). All lesions were located in the submucosa, but in 48% of cases, they also extended into the muscularis propria (Fig. 2-E). This phenomenon was more frequent in patients with a history of autoimmune diseases ($p = 0.042$, Fisher's exact test). The inflammatory cells were mainly eosinophilic granulocytes. Their average concentration was 60 ± 49/HPF (range: 15–200), and they were significantly more concentrated in IFPs larger than 2 cm in size ($p = 0.018$, Wilcoxon test) and in cases with mutations in the *PDGFRA* gene ($p = 0.033$, Wilcoxon test). Diffusely interspersed lymphocytes and plasma cells were also present but in a lower amount. IgG-positive plasma cells were observed in 83% of cases with an average of 33 ± 44/HPF (range: 3–160) and IgG4-positive plasma cells in 69% cases with an average of 17 ± 31/HPF (range: 1–110). Cases 1, 3, and 23 (10.3% of the total) showed an unusually high concentration of IgG-positive plasma cells (average: 140 ± 26/HPF, range: 110–160) and IgG4-positive plasma cells (average: 87 ± 21/HPF, range: 60–100), with an IgG4/IgG ratio greater than 0.4 (Fig. 3, Table 1). These cases occurred in the esophagus, stomach, and colon. The concentration of eosinophilic granulocytes was similar to that of the other IFPs (average: 67 ± 49/HPF; range: 20–100). Immunohistochemical expression of PDGFRA was present in six cases (20.1%) and significantly correlated with IFPs over 2 cm in size ($p = 0.030$, Fisher's exact test) (see Table 2).

In all but one case, the enhanced DNA was of sufficient quality. NGS analysis revealed gene sequence changes in 17 of 28 cases (60.7%), 64.7% of which occurred in the stomach, 17.6% in the small intestine, 11.8% in the colon, and 5.9% in the esophagus. The *PDGFRA* gene was mutated in 76.5% of cases, whereas 23.5% of cases revealed another mutation (of these, 66.6% did not have a *PDGFRA* mutation, and 33.3% had another mutation in addition to a *PDGFRA* mutation). The presence of mutations was also significantly correlated with IFPs greater than 2 cm in size ($p = 0.009$, Wilcoxon test). In eight gastric cases with *PDGFRA* mutation in exon 18 and amino acid exchange, the p.Asp842Val mutation was seen in six cases and exon 12 mutation in two cases (Table 1). In all three small intestine samples, the *PDGFRA* changes were solely located in exon 12. One sample revealed a point mutation, and the other two cases had an identical complex delins at position p.Ser566_Glu571. The IFPs with genetic aberrations in the colon and esophagus samples showed a very different profile, without changes in *PDGFRA* but mutations in *KRAS*, *BRAF*, *PIK3CA*, and *EGFR*.

Exon 12 of the *PDGFRA* gene was mutated in five of 13 cases (29.4% of all analyzed). Two of these cases revealed a mutation in Val561Asp in the stomach and small intestine, and two other cases indicated a mutation of Ser566_Glu571delinsArg occurring in the small intestine. Importantly, immunohistochemical expression of *PDGFRA* was present in 38% of cases (Table 4). This expression was significantly correlated with the mutations of the same gene presented in only IFP with mutation in exon 12 ($p = 0.005$, Fisher's exact test) (Table 1, Fig. 2F).

A total of 113 cases with a documented mutation were found in the literature. In the literature, all but one IFP occurred in the GIT, with the other one reported in the gall bladder [58]. Additionally, 77 IFPs (68%) in the literature revealed a mutation in the *PDGFRA* gene (Supplement Table 2). Exon 18 was most frequently mutated in the stomach (with 80.0% of cases having *PDGFRA* mutation), whereas exon 12 mutation was associated with intestinal onset (with 82.6% of cases having *PDGFRA* mutation) (Table 3). With regard to the codons being mutated, a similar result was observed between our cases and those reported in the literature. In exon 12, codons 566–571 were most frequently affected, whereas the mutation in exon 18 affected codons 842–846, with the highest frequency in 842 (Table 4).

4. Discussion

An IFP is a benign fibroblastic hypocellular lesion that develops most frequently in the antrum and ileocolic area but can occur in any part of

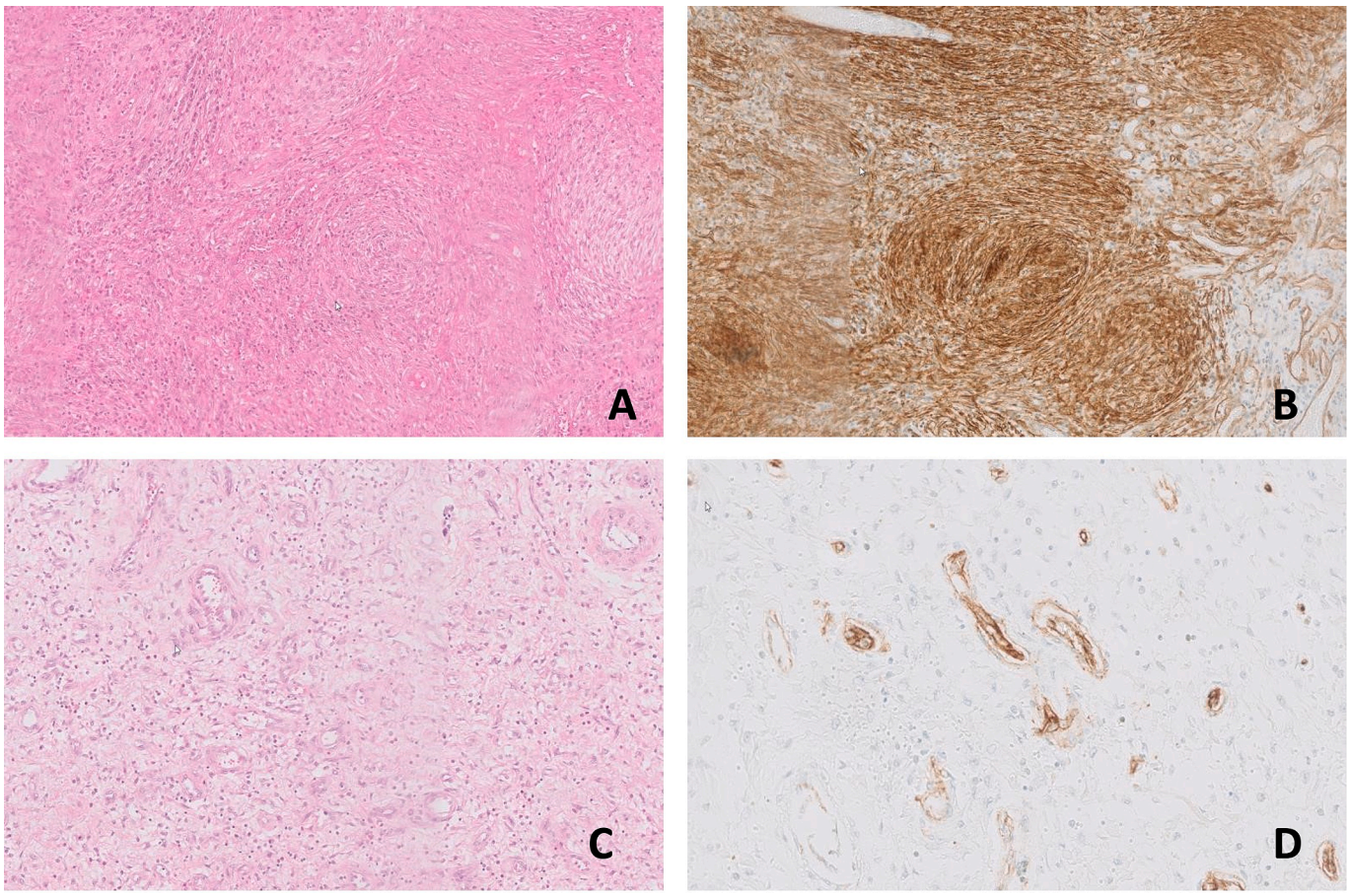

Fig. 1. IFP of the stomach (case 24) with typical onion-skin-like pattern of the spindle cells (A) and reactivity for CD34 (B); IFP of the ileum (case 17) without concentric arrangement of the spindle cells (C) and absence.

the GIT [3]. They frequently feature peculiar spindle cells and stellate cells with small or no visible nucleoli and a slightly eosinophilic cytoplasm [3]. Stromal cells reveal a concentric arrangement around blood vessels in an onion skin-like pattern and express positivity for CD34 [8]. In our cases, lesions arising in the stomach and esophagus showed higher cellularity (CD34-positive cells and lymphocytes) than intestinal ones. The lesions were interspersed mainly with eosinophilic granulocytes and, to a lesser extent, with lymphocytes and plasma cells [3]. Ki67 was low, indicating a slow growth process without necrosis [3,19]. IFPs are often described as localized in the submucosa up to the epithelium, and almost half of them cross the muscularis propria [20]. Nevertheless, in our 14 cases, 48% showed an invasion of the muscularis propria. This phenomenon has also been reported in the literature [21–23].

The etiology of IFPs is currently still uncertain [1], but they are believed to be of either fibroblastic or inflammatory origin [8] or triggered by microorganisms such as *Helicobacter pylori* and *Cytomegalovirus* [24,25]. Ricci et al. [26] suggested a pathogenic relationship to telocytes; telopodes, a newly discovered interstitial cell type with long, thin cytoplasmic processes; and positivity for *PDGFRA* and CD34 [26]. Telocytes may therefore be part of a common pathogenic pathway for *PDGFRA*-mutated IFPs as well as GISTs [26]. The discovery of activating mutations in the *PDGFRA* gene have strengthened the hypothesis of its triggering role in the initiation or enlargement of IFPs [8]. *PDGFRA* is a receptor on the cell membrane of several cell types [27]. Through binding to it, PDGF initiates a stimulating intracellular signaling pathway that induces cell growth and differentiation [28,29]. Single point mutations are the most common *PDGFRA* mutations and very similar to those first detected in GISTs [30,31]. These have been identified primarily in exon 18 and with lower abundance in exon 12 [31]. Mutations in this gene have been associated with somatic and familial GISTs as well as IFPs [9,32]. In exon 18, the most common is the activating point mutation c.2664A>T, which leads to a change in the p.Asp842Val amino acid; this plays an important role in the resistance mechanism of tyrosine kinase inhibitor treatment [13]. Almost all point mutations identified in *PDGFRA* exon 12 are represented by c.1821T>A, resulting in a p.Val561Asp change at the protein level. This mutation is the second most common substitution found in *PDGFRA* in GISTs [13]. In-frame deletions are also quite common in *PDGFRA*. These mutations have been identified in exon 18 and 12 and tend to cluster between codons p.40–848 in exon 18 and p.559–572 in exon 12. These types of mutations have been shown to activate *PDGFRA in vitro* and *in vivo* [30,31]. In general, *PDGFRA* mutants show a very low mitotic rate and a good prognosis in GIST [33,9,34]. *PDGFRA* is also mutated in several diseases, such as certain forms of hypereosinophilic syndrome [14], and in glioblastomas [35]. A strong association has been found between localization of IFPs in the GIT and the exon mutation of the *PDGFRA* gene [10]. In our cases, the mutated *PDGFRA* exon was associated with tumor localization, as previously shown in the literature [10]. Exon 18 was more often involved in gastric forms, while exon 12 was involved in small intestine forms (Tables 3 and 4). Moreover, in our cases, lesions with the mutation showed a larger size compared to wildtype lesions. In addition to *PDGFRA* changes, Case 18 showed an activating *PIK3CA* mutation at amino acid p.His1047Arg, which is a common hotspot variant in colorectal cancer [36], and Case 19 revealed activating *KRAS* (p.Gly12Ala), *TP53* (p.Arg175His), and *APC* (p.Arg1450Ter) mutations, which are described as the classical mutations in colorectal cancer evolution leading to chromosomal instability carcinogenesis [37].

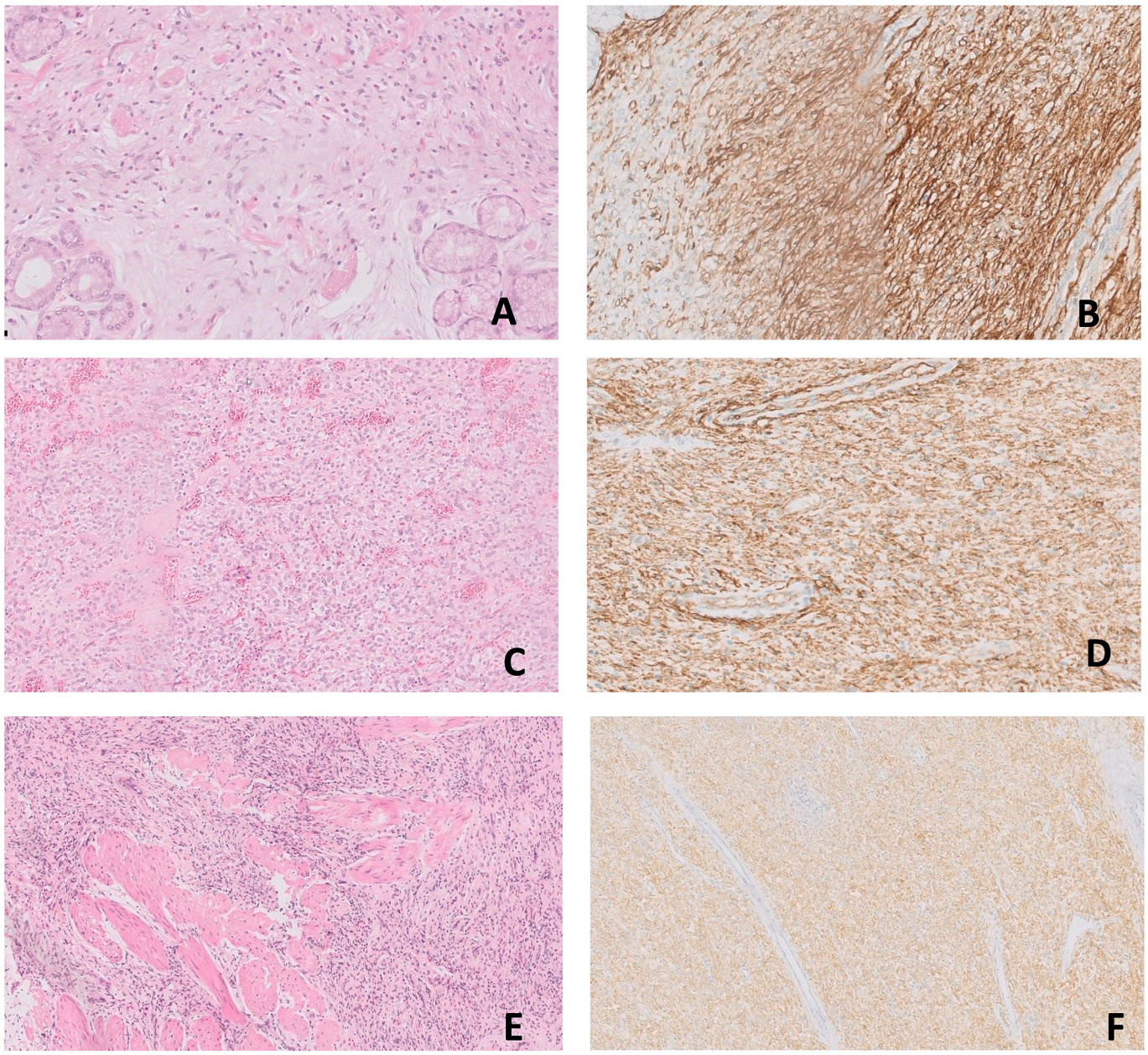

Fig. 2. Two cases of IFP of the stomach (case 13, A and B; case 19, C and D) with epithelioid cells in H&E and with reactivity for CD34; IFP of the stomach (case 28) with extensive involvement of the muscularis propria (E); IFP of the stomach (case 23) with mutation of exon 12 of the PDGFRA gene and positivity in histological staining (F).

Six of 29 patients (21%) show mutations other than PDGFRA. These are three men and three women with a mean age of 61 ± 15 (45–86). We believe that our case series is too small to assume significant associations between these mutations and clinical data such as gender, age or location of tumor. In our opinion, this is certainly an important aspect that should be investigated in further studies as it could provide further information on possible links with other tumors.

A differential diagnosis of IFP includes mesenchymal lesions with spindle cell cytomorphology being infiltrated with eosinophilic granulocytes. According to the gastrointestinal localization, the most frequent type is GISTs with spindle cell morphology that develop in the muscularis propria and do not show eosinophilic granulocytes [38,39]. Both GISTs and IFPs express CD34 in about 10% and harbor mutations of the *PDGFRA* gene up to 30–50% [31]. The epithelioid cell morphology occurs in gastric IFPs and in up to 25% of gastric GISTs (Fig. 2) [33]. Despite some morphological similarities between the two entities, expression of CD117 and the more specific expression of *DOG1* are decisive for GISTs [11,3]. In other spindle cell tumors, S100 positivity, as in schwannomas and neurofibromas, or SMA and desmin positivity in leiomyomas can be helpful, as they are negative in IFPs [11]. Another differential diagnosis is the solitary fibrous tumor that also occurs in the GIT and exhibits CD34 positivity. However, *NAB2-STAT6* gene rearrangement [40], a much more abundant and hypercellular fibrous stroma, perivascular hyalinization, and the presence of multinucleated stromal cells are compatible with the diagnosis of solitary fibrous tumors [41]. Inflammatory myofibroblastic tumors differ histologically from IFPs, as the former are comprised of myofibroblastic stellate cells with prominent nucleoli and scattered mitoses [42]. The spindle cells may show a sturgeon or fascicular pattern but generally show higher cellularity than IFPs. Unlike IFPs, they do not show CD34 positivity but do show expression of *ALK*, *ROS1*, or *NTRK3* [43]. However, negativity when staining with CD34 and the absence of spindle cells does not

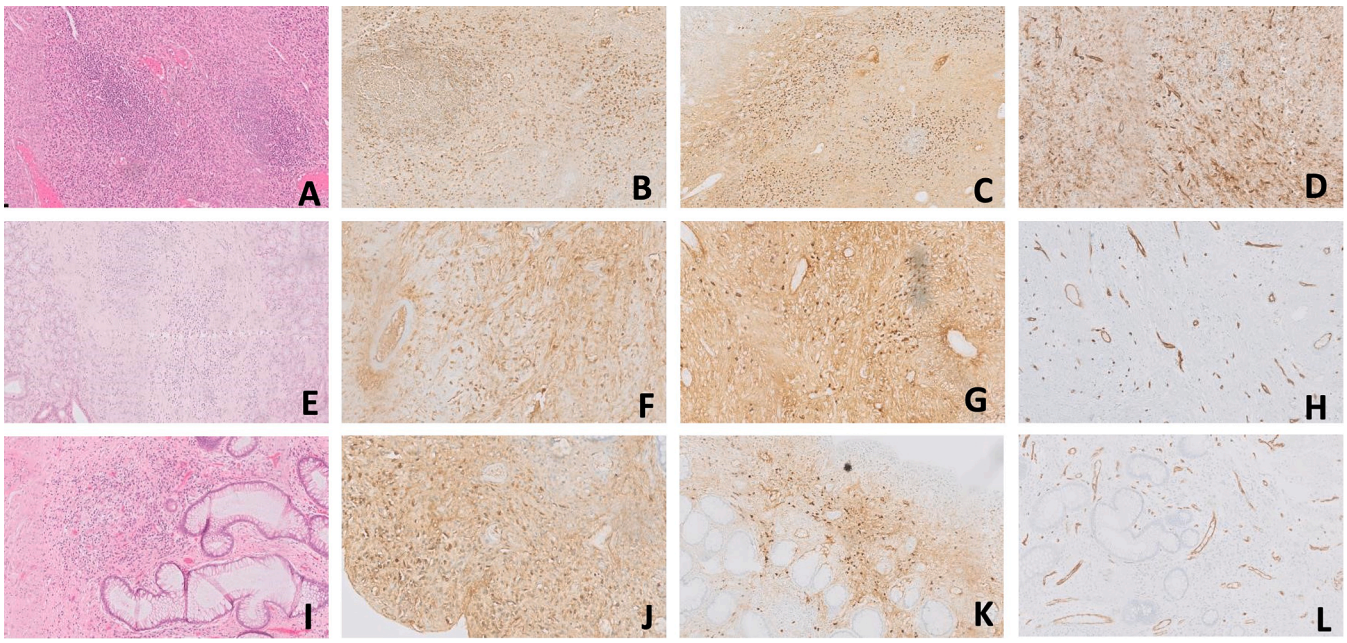

Fig. 3. IFP of oesophagus (case 2, A) with numerous IgG (B), IgG4 (C) and reactivity for CD34 (D); IFP of stomach (case 1, E) with numerous IgG (F), IgG4 (G) and negativity for CD34 (H); IFP of colon (case 3, I) with numerous IgG (J), IgG4 (K) and negativity for CD34 (L).

Table 2
Correlation between PDGFRA mutation using new generation sequencing and immunohistochemical PDGFRA expression.

	sophagus		Stomach		Small Intestine		Colon	
	n	expression	n	expression	n	expression	n	expression
exon 12	0	0	2	2	3	3	0	0
exon 18	0	0	8	1	0	0	0	0
WT	0	0	6	0	0	0	5	0
others	2	0	4	0	0	0	3	0

Table 3
Exon mutation spectrum of PDGFRA gene in 140 gastrointestinal inflammatory fibroid polyps (112publishedand28owncases).

	Esophagus			Stomach			Small intestine			Colon			Total
	own	publ.	**all**	own	publ.	**all**	own	publ.	**all**	own	publ.	**all**	
PDGFRA wt	1	0	**1**	7	24	**31**	0	8	**8**	7	3	**10**	**50**
PDGFRA mut	0	0	**0**	10	31	**41**	3	45	**48**	0	0	**1**	**90**
exon 2	0	0	**0**	0	0	**0**	0	1	**1**	0	0	**0**	1
exon 10	0	0	**0**	0	3	**3**	0	1	**1**	0	0	**0**	**4**
exon 12	0	0	**0**	2	8	**10**	3	38	**41**	0	0	**0**	**51**
exon 14	0	0	**0**	0	0	**0**	0	1	**1**	0	0	**0**	**1**
exon 18	0	0	**0**	8	20	**28**	0	4	**4**	0	1	**1**	**33**

exclude the presence of an IFP with absolute certainty [32].

Interestingly, in three of our 29 cases, we found an unusually high positivity of IgG4 plasma cells, a typical phenomenon in the family of IgG4-related diseases (IgG4-RDs) (Fig. 3). IgG4-RD is a chronic inflammatory condition characterized by infiltrate composed largely of B and T lymphocytes and IgG4 plasma cells with storiform fibrosis and occasionally obliterative phlebitis [44]. IgG4-RD encompasses a wide spectrum of manifestations that can involve any organ singularly or be multisystemic [45]. IgG4-RD involvement has also described in many different sites, such as the pancreas, biliary tract, lymph nodes, periorbital tissues, retroperitoneum, kidneys, aorta, mediastinum, lungs, meninges, and the entire GIT [46,47]. Considering this enormous variety of localizations, it is not surprising that IgG4-RD or IgG4-RPT can present unusual morphological presentations that mimic other diseases or even malignant lesions [48–51]. In particular, although storiform fibrosis was not observed, three of our cases showed an IgG4/IgG ratio of more than 0.4, the threshold proposed by Deshpande et al. for the diagnosis of IgG4-RD [52]. Furthermore, among the pathogenetic mechanisms underlying fibroblastic activation, a direct role has been hypothesized for B cells through PDGF expression [53,54]. A variable number of eosinophils has been described in IgG4-RD [55,53]. Only one of our three cases showed reactivity to histological staining for *PDGFRA*, while in two cases, NGS did not detect a mutation. In one case, molecular analysis by NGS was unfortunately not possible due to insufficient DNA. A possible link between IgG4 plasma cells and eosinophilic granulocytes has already been described in other diseases such as chronic rhinosinusitis [56] and eosinophilic esophagitis [57]. However, in the differential diagnosis the absence of lymphoplasmacellular infiltrate and storiform fibrosis makes IgG4-RPT very improbably.

Conclusively, our study confirms the correlation of *PDGFRA* gene mutation in exon 12 with small intestine-type IFPs and mutation in exon 18 with gastric-type IFPs. *PDGFRA* expression was significantly

Table 4
Codon mutation spectrum in exon 12 and 18 of PDGFRA gene in 84 gastrointestinal inflammatory fibroid polyps.

Exon		Codon			Stomach			Small Colon			Total intestine
		own	publ.	all	own	publ.	all	own	publ.	all	
Exon 12 (n = 51)	556	0	1	**1**	0	0	**0**	0	0	**0**	**1**
	557	0	1	**1**	0	1	**1**	0	0	**0**	**2**
	558	0	1	**1**	0	1	**1**	0	0	**0**	**2**
	559	0	2	**2**	0	1	**1**	0	0	**0**	**3**
	560	0	3	**3**	0	1	**1**	0	0	**0**	**4**
	561	1	4	**5**	1	2	**3**	0	0	**0**	**8**
	562	0	2	**2**	0	1	**1**	0	0	**0**	**3**
	563	0	2	**2**	0	1	**1**	0	0	**0**	**3**
	564	0	2	**2**	0	0	**0**	0	0	**0**	**2**
	565	0	2	**2**	0	0	**0**	0	0	**0**	**2**
	566	1	6	**7**	2	36	**38**	0	0	**0**	**45**
	567	1	6	**7**	2	36	**38**	0	0	**0**	**45**
	568	1	5	**6**	2	36	**38**	0	0	**0**	**44**
	569	1	5	**6**	2	36	**38**	0	0	**0**	**44**
	570	1	5	**6**	2	36	**38**	0	0	**0**	**44**
	571	1	5	**6**	2	36	**38**	0	0	**0**	**44**
	572	0	1	**1**	0	1	**1**	0	0	**0**	**2**
	573	0	0	**0**	0	1	**1**	0	0	**0**	**1**
	591	1	0	1	0	0	0	0	0	**0**	1
Exon 18 (n = 33)	824	0	1	**1**	0	0	**0**	0	0	**0**	**1**
	842	7	19	**26**	0	4	**4**	0	1	**1**	**31**
	843	1	4	**5**	0	0	**0**	0	0	**0**	**5**
	844	1	3	**4**	0	0	**0**	0	0	**0**	**4**
	845	1	3	**4**	0	0	**0**	0	0	**0**	**4**
	846	1	1	**2**	0	0	**0**	0	0	**0**	**2**
	847	0	1	**1**	0	0	**0**	0	0	**0**	**1**
	848	0	1	**1**	0	0	**0**	0	0	**0**	**1**

correlated with a mutation in exon 12 of the same gene. These data refer to a possible trigger role of expression and mutation in exon 12 of *PDGFRA* in the progressive enlargement of IFPs. The data also indicate different pathways of origin. Thus, the spectrum of differential diagnoses of fibrous lesions with eosinophilic granulocytes in three of our cases revealed an overlapping histo-morphology with IgG4-RPT. However, IFPs are a distinct different entity but IgG4-RPT have to be excluded because they display a potential differential diagnosis with therapeutic implications.

Ethical Approval Statement

Use of the tissues was approved by the local ethics committee in Munich (Reference number 21-1191).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpr.2023.300703.

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