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Review Article

Dedifferentiated gastrointestinal stromal tumor: Recent advances

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal lesions of the gastrointestinal tract. A small minority of GISTs exhibit morphologic and phenotypic changes and differentiate into an unusual phenotype through the process of dedifferentiation. Dedifferentiation can occur either *de novo* or after prolonged treatment with imatinib, a selective tyrosine kinase inhibitor. GISTs can present with various morphologies including rhabdomyosarcoma, angiosarcoma, or undifferentiated pleomorphic sarcoma. The unusual histologic and immunohistochemical characteristics of these tumors can be diagnostically challenging. Therefore, it is essential that the pathologists recognize GISTs with unusual morphology and be aware of the dedifferentiation process.

This review aims to provide an overview of the morphologic and molecular features of dedifferentiated GISTs. Additionally, we discuss diagnostic dilemmas and recent immunohistochemical markers that are useful in distinguishing dedifferentiated GISTs from other gastrointestinal tumors.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. It is widely accepted that they originate from or differentiate into interstitial cells of Cajal (ICC), which function as pacemaker cells for peristaltic contractions. GISTs usually exhibit monotonous morphology characterized by uniform cells with minimal cytologic atypia, rare mitoses, and immunoreactivity for CD117, which is encoded by the *KIT* gene [1]. Most tumors occur in the stomach, followed by the small intestine, and the esophagus or rectum [2]. GISTs have also been rarely reported in the appendix and gallbladder [3,4]. GISTs may rarely appear at extravisceral locations, such as the mesentery, pelvis, omentum, and retroperitoneum. Tumors appearing in the previous locations are named "extragastrointestinal GISTs" [5].

Occasionally, GISTs may exhibit morphologic and phenotypic changes and differentiate into an unusual phenotype through the process of dedifferentiation. Dedifferentiation is a cellular process reverting cells to a less differentiated stage. Dedifferentiation involves loss of lineage-specific gene expression and regression from a specialized tissue to a primitive state of development [6-8]. It usually occurs during tumor initiation and is correlated with tumor progression [9]. In 1971, Dahlin and Beabout first defined the term "dedifferentiation" to describe a low-grade chondrosarcoma associated with high-grade nonchondrogenic sarcoma components [10]. Pauwels et al. initially used the term "dedifferentiation" for GISTs, and defined it as an abrupt transition from a conventional KIT-positive GIST to a high-grade KIT-negative tumor alongside loss of the histologic characteristics of the primary tumor [11]. Dedifferentiation plays an important role in cell immortality causing resistance to therapy in recurring and metastatic tumors [12]. Until recently, dedifferentiated anaplastic variants of GISTs were reported only in patients who had received long-term treatment with the tyrosine kinase inhibitor imatinib mesylate [11,13,14]. More recently, however, cases of *de novo* dedifferentiated GISTs, irrespective of treatment with a therapeutic agent, were reported. These tumors can be diagnostically challenging due to their obvious anaplastic appearance and lack of CD117 expression [15,16]. Early diagnosis of dedifferentiation can significantly enhance the treatment and management of the patients. Clinicopathological correlation, radiological findings, immunohistochemical studies, and molecular analyses are often required to characterize dedifferentiated GISTs.

In this review, we highlight the dedifferentiation mechanisms in GISTs and provide an overview of the morphologic and molecular features of dedifferentiated tumors with emphasis on the recent literature and the advances in molecular diagnostic tools. Possible pitfalls and diagnostic dilemmas are also reviewed.

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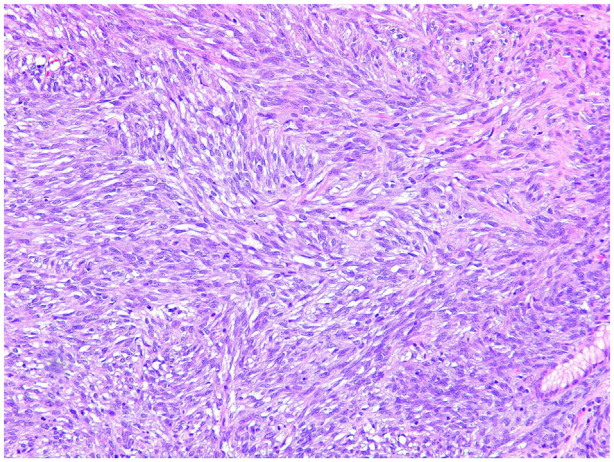

Fig. 1. Gastrointestinal stromal tumor (GIST) shows uniform spindle cells with inconspicuous nucleolus and lack of or low mitotic activity [hematoxylin and eosin (H&E), ×100].

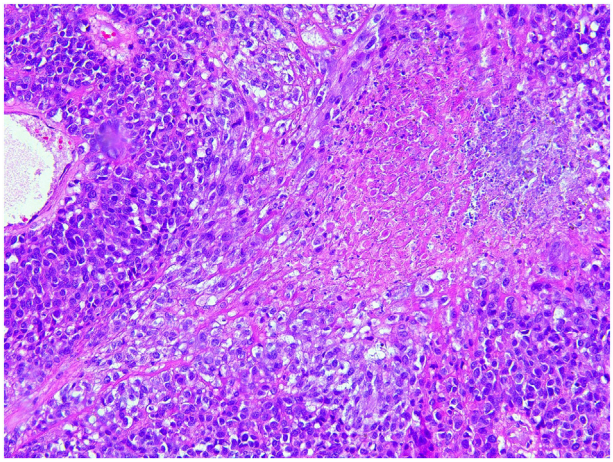

Fig. 3. Dedifferentiated GIST with large area of necrosis (H&E, ×40).

2. Microscopic features

GISTs are divided into main subtypes based on their morphological features [17]. The majority (70%) are spindle cell GISTs composed of fusiform cells with scant, fibrillary eosinophilic cytoplasm and ovoid nuclei arranged in intersecting, ill-defined fascicles or whorls [15,17,18]. The nuclei are uniform with evenly distributed chromatin and inconspicuous nucleoli and exhibit low mitotic activity (Fig. 1). Pleomorphism is very rare but may occur in areas with hemorrhagic necrosis [19]. Less common epithelioid (8%) and mixed variants (15%) have also been reported [20]. The epithelioid variant is more frequently found in the stomach and omentum [19,21]. GISTs are variably cellular. Sclerotic, myxoid and collagenous stromal changes can be seen regardless of the cell morphology [18]. In general, GISTs are characterized by three important features: a) uniform and monotonous appearance, b) rare mitoses, and c) fusiform nuclei. Therefore, tumors exhibiting increased cellularity with significant pleomorphism, numerous mitoses, and long slender nuclei should prompt consideration of the possibility of other types of sarcomas or dedifferentiated GISTs (Fig. 2).

The dedifferentiated component, which is rarely seen in GISTs, is morphologically distinct from the classical GIST. The dedifferentiated component presents anaplastic/pleomorphic appearance, high nuclear atypia, high mitotic activity, and necrosis (Figs. 2 and 3), multinucleated neoplastic giant cells can be seen, but are not necessarily present [16,22]. The dedifferentiated component can appear in various histological patterns. Pauwels et al. first reported two cases of clinically progressive GISTs and one case of a stable tumor treated with imatinib. During treatment, the above tumors exhibited diffuse epithelioid or pseudopapillary epithelioid growth patterns characterized by rounded cells with eosinophilic cytoplasm and round-to-oval nuclei in contrast to primary, conventional spindle-type GISTs [11]. Alteration of the morphology to a “dedifferentiated phenotype” not only included the loss or significantly decreased KIT immunoreactivity (Fig. 4) but the aberrant expression of epithelial and muscle markers, such as desmin in the recurrent tumor. The morphology of the lesions differed from that of the primary tumors in all three previous cases [11]. More recently, Liegl et al. reported five cases of progressive metastatic GISTs with rhabdomyoblastic differentiation [14]. The rhabdomyoblastic areas comprised two different components: 1) spindle cells with round and oval vesicular nuclei, focally prominent nucleoli, and abundant eosinophilic cytoplasm with an elongated shape “tadpole configuration” resembling embryonal rhabdomyosarcoma; and 2) spindle cells mixed with large atypical, occasionally multinucleated polygonal cells, and bright eosinophilic cytoplasm, resembling pleomorphic rhabdomyosarcoma. In these cases, the tumor areas with rhabdomyoblastic differentiation (Fig. 5) were adjacent to the areas with classic GIST morphology [14]. Immunohistochemical staining with desmin, MyoD1 (Fig. 6), and myogenin was used to confirm rhabdomyoblastic differentiation in metastatic tumors. Other similar cases of metastatic GISTs

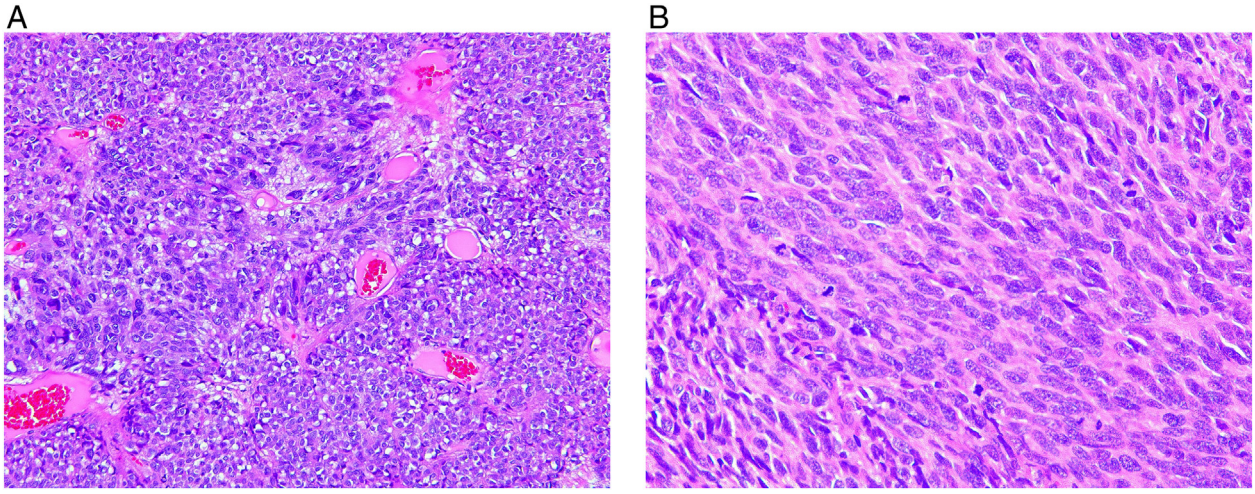

Fig. 2. Dedifferentiated GIST with pleomorphism (2A) and numerous mitoses (2B) (H&E, ×100).

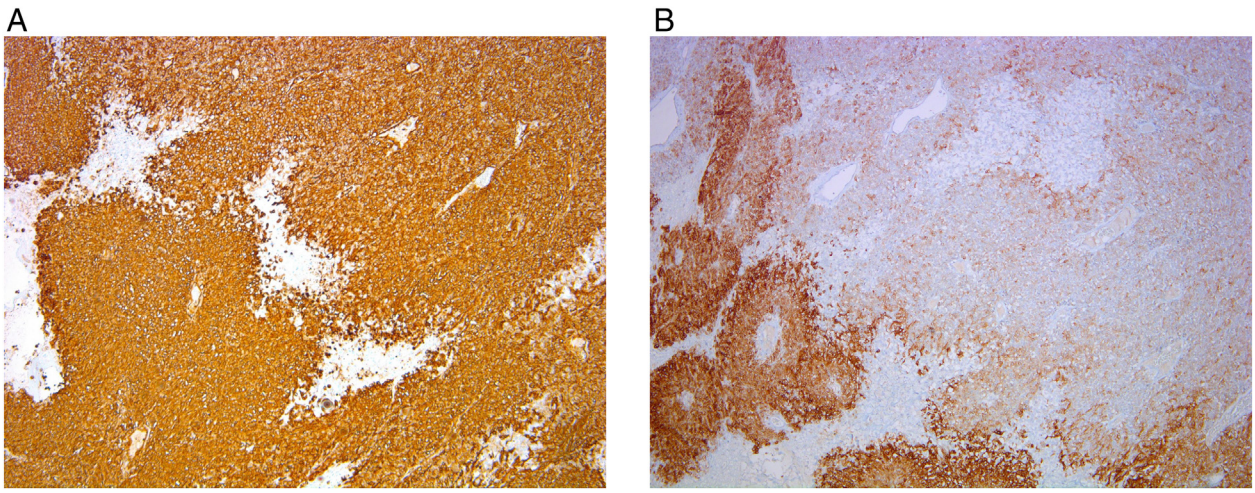

Fig. 4. C-kit immunostain in classic GIST with diffuse and strong positivity (4A) and in dedifferentiated GIST with loss of or significantly decreased c-kit immunoreactivity (4B) (c-kit immunostain, ×100).

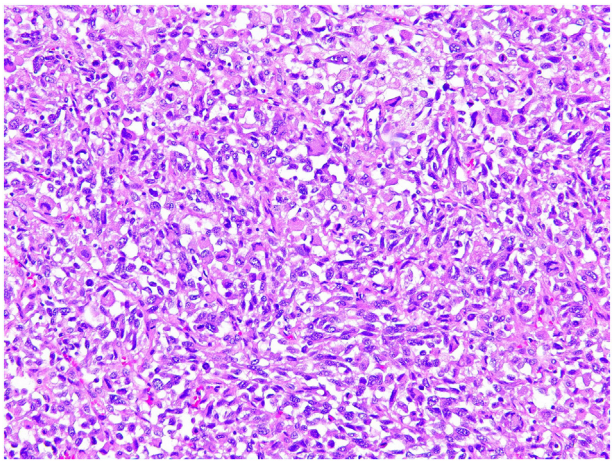

Fig. 5. Dedifferentiated GIST with rhabdomyosarcomatous component with tumor cells showing eccentric nuclei and eosinophilic cytoplasm (H&E, ×100).

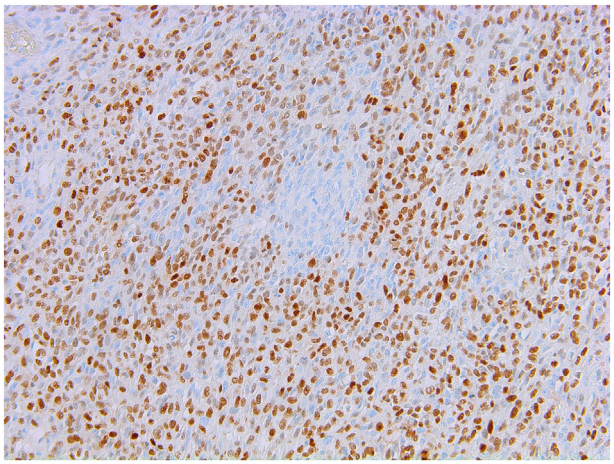

Fig. 6. MyoD1 immunostain shows nuclear positivity in rhabdomyosarcomatous component of dedifferentiated GIST (MyoD1 immunostain, ×100).

with rhabdomyosarcomatous differentiation have also been reported [22,23].

Classic GIST can also dedifferentiate into a pleomorphic sarcoma, either *de novo* or after imatinib treatment [24,25]. Histologically, the area of pleomorphic sarcoma usually demonstrated a sharp transition from the classical GIST component (Fig. 7) corresponding to the grayish-white and pinkish areas of the gross specimen. The dedifferentiated component was highly cellular with marked pleomorphism and had frequent mitoses [24]. Also, necrotic areas were frequently seen. Dedifferentiated areas were composed of proliferated, spindly fibroblastic cells, multinucleated giant cells, histiocytes, and pleomorphic cells showing loss of c-kit, DOG1, and CD34 expression [25]. Similarly, Antonescu et al. [16] reported eight cases exhibiting spindle cell and dedifferentiated components, and pleomorphic sarcoma phenotype. In this study, one tumor showed an unprecedented angiosarcoma phenotype with hyperchromatic and anaplastic tumor cells forming irregular, anastomosing slit-like vascular spaces. Interestingly, our case of dedifferentiated GIST showed preservation of CD34 with loss of c-kit and DOG1 (Fig. 8). This discrepancy requires further studies with more cases. CD31 was used to highlight the irregular vascular spaces and confirm the diagnosis [16]. Notably, the patient had a history of treatment with imatinib. In the previous studies, the authors did not report any remarkable morphologic difference between the dedifferentiated components occurring *de novo* or after imatinib therapy [16]. It is clinically significant to note that dedifferentiation mostly occurred in metastatic or recurrent lesions [11,14,16]. However, Jung et al. reported the case of a dedifferentiated GIST where the conventional GIST component had metastasized to the regional lymph nodes and liver [25]. Given these observations, the biological behavior and clinical significance of dedifferentiated component remains to be elucidated.

3. Immunohistochemical findings

Approximately 95% of classic GISTs typically express CD117 [26-28] and CD34 in about 60–70% of the lesions (Figs. 4A and 8A). Less commonly, they demonstrate positive staining for smooth muscle actin (SMA) (30–40%), S-100 protein (5%), and desmin or keratin (1–2%) [19]. The KIT staining pattern varies from cytoplasmic to membranous, and it usually is diffuse and intense. Occasionally, a paranuclear “dot-like” staining pattern is also seen [18]. Although CD117 is the best-known diagnostic marker for GISTs, approximately 5% of GISTs are negative for KIT by immunohistochemistry [29]. Additionally, concomitant *de novo* expression of cytokeratin and desmin has been variably reported [13,14,16]. Several highly sensitive and specific markers that were recently discovered have improved diagnosis of GISTs, primarily KIT-negative cases.

A relatively new promising biomarker was discovered on GIST-1

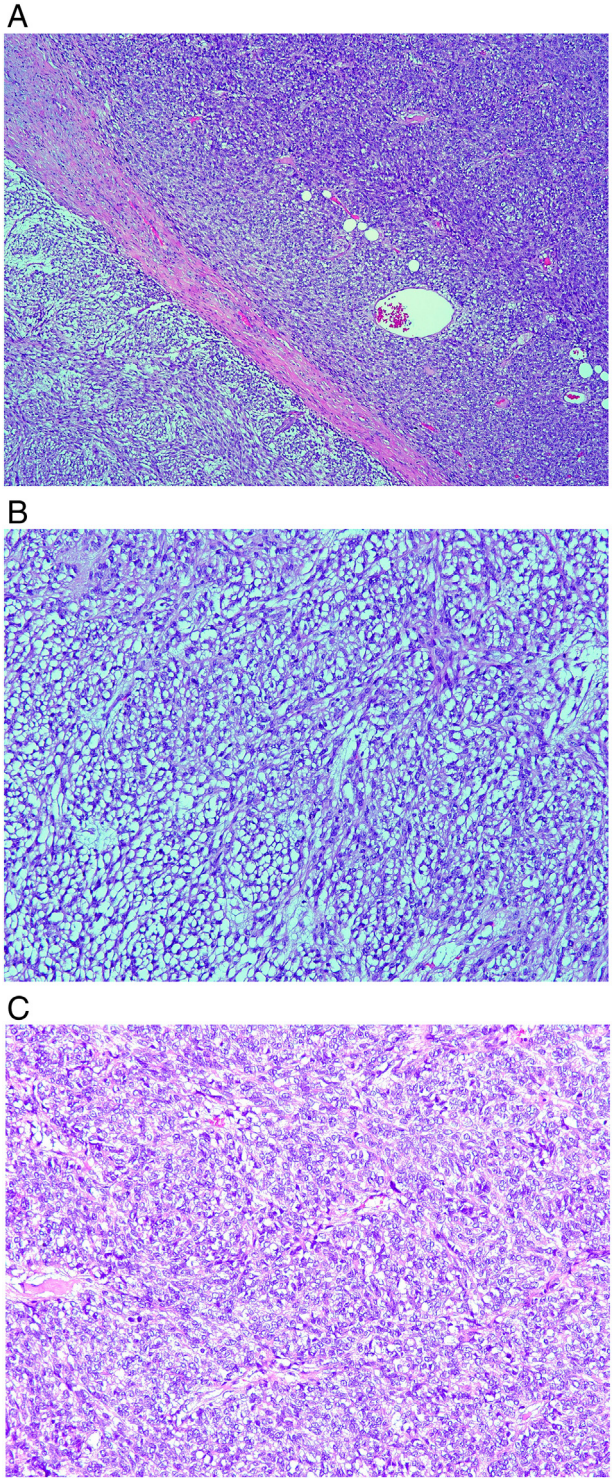

Fig. 7. A. Dedifferentiated GIST with high cellularity (upper field) with sharp transition from classic GIST (low field) (H&E, ×40). High power of classic GIST (7B) and dedifferentiated GIST (7C).

(DOG1) (Fig. 9), a calcium-activated chloride channel protein. DOG1 is specific and sensitive for both KIT-negative and -positive GISTs [18,30,31]. Sensitivity of DOG1 in detecting GISTs varied from 75 to 100% depending on the type of antibody used [32-35]. Clone K9 (detecting expression of DOG1) showed the highest sensitivity and specificity for both KIT-positive and -negative tumors [36]. Several studies showed that DOG1 is also useful in detecting KIT-negative GISTs, particularly those of gastric origin, with epithelioid morphology or harboring the platelet-derived growth factor receptor (*PDGFRA*) mutation [30,31,37]. The immunohistochemical findings were also confirmed by *in situ* hybridization using DOG1, KIT, and PDGFRA probes [37]. On the other hand, DOG1 expression was detected in KIT-negative tumors that were wild-type for *KIT* and *PDGFRA* by mutation analysis [30]. Thus, for patients with unusual GIST features and loss of CD117 expression, DOG1 immunostaining should be preferably performed. Choi et al., however, detected loss of DOG1 in the anaplastic component of a *de novo* dedifferentiated GIST, the largest tumor reported to date in the small intestine (diameter 30 cm) [15]. Therefore, the last European consensus suggested the use of mutational analysis in cases exhibiting negative staining for both CD117 and DOG1 [38]. In the reported cases, ICC was used as a positive internal control to evaluate CD117 and DOG1 expression [33,37].

Protein kinase C theta (PKC θ) is another novel diagnostic immunohistochemical marker for GIST [39]. PKC θ is a member of the serine/threonine family of protein kinases and is selectively expressed in the ICC lineage. Kang et al. reported PKC θ immunoreactivity in most KIT-negative tumors, regardless of *KIT* and *PDGFRA* mutational status of the tumors [30]. In the study, the majority of cases were positive for both DOG1 and PKC θ in all KIT-negative GISTs. Moreover, PKC θ was positive in two cases lacking expression of both KIT and DOG1. The expression of both DOG1 and PKC θ in KIT-negative tumors was higher than that in the KIT-positive group, but the difference was not statistically significant [30]. PKC θ is a specific marker that is useful for the differential diagnosis of GIST from other mesenchymal tumors [39,40]. The staining intensity of PKC θ varies and usually is diffuse and cytoplasmic; however, it shows a more membranous staining pattern in epithelioid cells. In a few studies, the authors suggested that PKC θ is not a useful diagnostic biomarker due to its background staining and low reproducibility [17,39-41]; however, several others have suggested the use of combined staining for DOG1 and PKC θ as a promising diagnostic tool, particularly in KIT-negative GISTs [30].

Recently, a new antibody, carbonic anhydrase II (CAII), was introduced as a diagnostic marker of GISTs [42]. Irrespective of mutational status, it is highly expressed in 95% of GISTs and about 50% of KIT-negative cases [42]. Prognosis of GISTs with high CAII levels was better than that of tumors with low or lacking expression of the marker. These findings indicate that CAII could serve as a diagnostic and prognostic biomarker [42,43]. Further studies are required to validate the use of CAII as a prognostic biomarker.

4. Molecular studies

GISTs arise from precursors of ICC *via* activation of *KIT* or *PDGFRA* gene mutations [28,44,45]. *KIT* or *PDGFRA* mutations, which occur through upregulation of downstream signaling pathways including RAS/RAF/MAPK, are the initiating events in the pathogenesis of most GISTs. The previous mutations result in ligand-independent phosphorylation and constitutive activation of several signaling pathways such as cell proliferation, apoptosis, and differentiation [17,46,47]. Approximately 10–15% of GISTs carry *PDGFRA* mutations [45]. *PDGFRA* is structurally similar to the *KIT* gene, and its mutations result in ligand-independent kinase activation. *PDGFRA* mutations are mutually exclusive. The most common mutation site of the *KIT* gene is located in exon 11 but mutations also occur in exons 9, 13, and 17 [48,49]. Mutations in the *PDGFRA* gene involve exons 12, 14, or 18 [18,50]. Alterations in exons can occur as point mutations, deletions, or insertions in the *KIT* or *PDGFRA* genes [50]. GISTs lacking mutations in either *KIT/PDGFRA* or *RAS* genes are considered wild-type GISTs. The most frequent molecular alterations in wild-type GISTs involve succinate dehydrogenase (SDH) deficiencies. SDH participates in the citric acid cycle and the electron transport chain [51]. More recently, *BRAF* exon 15 V600E mutations were identified in wild-type GISTs primarily found in the small intestine [52,53].

Molecular alterations in dedifferentiated GISTs can occur after

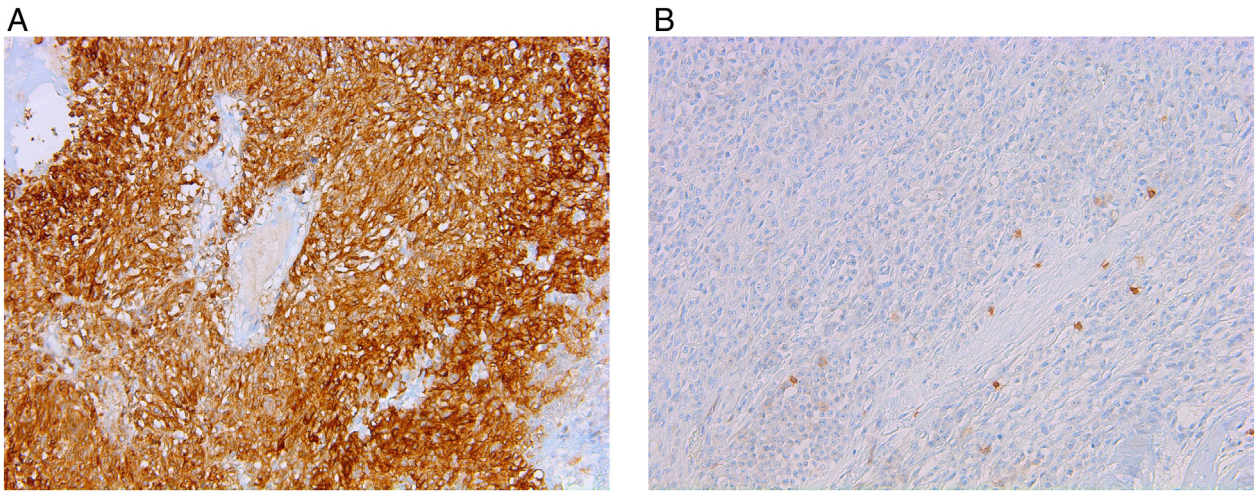

Fig. 8. Positive CD34 (8A) and negative c-kit immunostains (8B) are seen in dedifferentiated GIST (CD34 and c-kit immunostains, ×100). Note internal control positive cells of scattered mast cells.

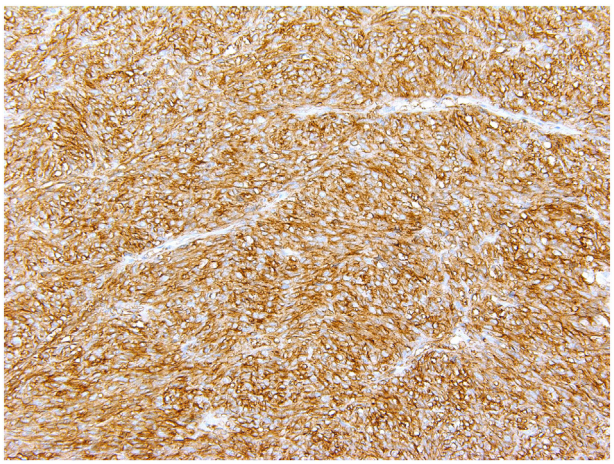

Fig. 9. DOG1 positive immunostain in GIST (DOG1 immunostain, ×100).

tyrosine kinase inhibitor treatment or develop *de novo*. Despite the fact that several recent studies have been conducted on the possible molecular mechanisms of dedifferentiation in GISTs, the secondary events involved in dedifferentiation have not been elucidated.

5. Dedifferentiation after therapy

Pauwels et al. first demonstrated the process of dedifferentiation in GISTs [11]. The authors showed the sharp phenotypic tumor alterations induced by KIT-independent mechanisms of resistance to tyrosine kinase inhibitors [11]. In this study, GIST dedifferentiation was defined as progression of the tumor from a classic KIT-positive GIST to an anaplastic/pleomorphic-type KIT-negative one. The authors presented three cases of dedifferentiated GISTs: two developed imatinib-resistant metastases and one had a stable lesion in the liver [11]. *KIT* mutational analysis revealed the presence of distinct exon 11 mutant isoforms in all cases. Similarly, Liegl and Jiang reported cases of metastatic GISTs with rhabdomyoblastic differentiation after chronic inhibition of KIT-signaling during imatinib therapy [14,22]. *KIT* exon 11 deletion [14], *KIT* exon 11 point mutation [14,22], and *PDGFR* exon 18 deletion [14] were detected in both classical and rhabdomyoblastic components. However, additional secondary mutations were not detected in dedifferentiated components, thus suggesting activation of alternative oncogenic pathways [14,22].

Antonescu et al. investigated the underlying molecular mechanism of tumor progression in three imatinib-resistant and five imatinib-naïve tumors [16]. Molecular characterization of the tumors showed that half of them had wild type *KIT*, *PDGFRA*, and *BRAF* genes in both conventional and dedifferentiated components in contrast to *KIT*-mutant GIST. These findings suggest that dedifferentiation can be triggered through alternative escape mechanisms besides activating mutations. Loss of a *KIT* gene copy due to haploinsufficiency was found in the dedifferentiated components of the three KIT-negative imatinib-resistant GISTs. Two imatinib-resistant tumors showed co-existence of *KIT* mutations in exons 11 and 13 [16]. In accord with the study reported by Jiang et al., these mutations were seen in both KIT-positive and -negative dedifferentiated tumor components [16]. Genetic instability, indicated by loss of heterozygosity (LOH) or low-level KIT amplification, was the most common finding in the dedifferentiated components [16]. Moreover, concurrent *KRAS* and *KIT* mutations were found in one KIT-negative GIST with anaplastic dedifferentiation after long-term imatinib therapy for chronic myelogenous leukemia (CML) [16]. It is unclear, however, if the *KRAS* mutation played a driver role in inducing this phenotype because other studies did not show mutational activation of *KRAS* in the patient cohort with GISTs [54].

6. *De novo* dedifferentiation

De novo dedifferentiated GISTs have only been reported in a handful of cases. It has been shown that dedifferentiation can occur *de novo* through KIT-independent mechanisms with loss of KIT expression and altered morphology [15,16,25]. In a recent multi-institutional study on these tumors, five out of eight dedifferentiated GISTs occurred *de novo* [16]. Molecular analysis demonstrated *KIT* mutations on exon 11 in three out of five cases. Remarkably, the other two patients had wild-type tumors with lower levels of KIT amplification as compared to that of the KIT-positive component with classic GIST morphology. The previous findings suggested that activation of alternative pathways driven by a KIT-independent oncogenic mechanism such as KIT promoter methylation or miRNA may play a role in KIT-negative dedifferentiated GISTs [16]. In 2013, Jung et al. reported another similar case of a GIST that dedifferentiated *de novo* to a pleomorphic sarcoma. *KIT* exon 11 mutation was detected by molecular analysis. There was no difference in *KIT* genotype between the two tumor components [25]. Choi et al. reported the largest *de novo* dedifferentiated GIST in the small intestine; activating mutations were not detected in the two distinct components of the tumor [15].

In summary, the process of dedifferentiation in combination with loss of KIT expression may not be associated with the occurrence of

additional mutations in the original driver oncogene. To the contrary, recent findings suggest alternative escape mechanisms driven by KIT-independent signaling pathways.

7. Diagnostic pitfalls and important tips

Dedifferentiated GISTs are diagnostically challenging because of their unusual histologic features and loss of KIT expression. The challenge is to determine whether the secondary tumor originated from mutations that morphologically altered the primary tumor or from a primary tumor that is completely unrelated to the previous tumor. Dedifferentiation of GISTs can occur regardless of imatinib therapy. Therefore, pathologists and clinicians should be familiar with the dedifferentiation process in GISTs and understand the underlying biology behind it.

There are certain diagnostic pitfalls regarding dedifferentiated GISTs that pathologists should be aware of:

- Clinically, GISTs may coexist with other malignancies. Due to alterations in the morphology and immunoprofile of the dedifferentiated component, a GIST may be easily misdiagnosed as a non-GIST sarcoma, such as pleomorphic sarcoma, rhabdomyosarcoma, or angiosarcoma [14,16,22]. It should be noted that the adjacent spindle cell component usually expresses GIST markers, despite the decreased expression of GIST markers in the dedifferentiated component. Therefore, adequate sampling of both conventional and dedifferentiated areas is essential in cases of conventional GISTs with unusual morphology [15].
- A potential pitfall involves the possible coexistence of a classical GIST with leiomyosarcoma. Diagnosis of primary leiomyosarcomas in the gastrointestinal tract is rare. Microscopically, leiomyosarcomas are composed of fascicles of spindle-shaped cells with bright eosinophilic cytoplasm and moderately large blunt-ended nuclei with focal or diffuse pleomorphism. Also, these tumors rarely show KIT immunoreactivity. Possible GIST dedifferentiation, previous GIST diagnosis, imatinib therapy, and adequate sampling should be considered for appropriate diagnosis [24].
- Non-random association of desmoid-type fibromatosis with GIST may be misdiagnosed as dedifferentiation [16]. Both tumors may show weak or negative expression of KIT and, if these tumors arise after imatinib therapy they could easily be misinterpreted as KIT-negative imatinib-resistant GISTs. However, the characteristic uniformly long fascicules of spindle cells within a collagenous or keloidal stroma and the vasculature may help to differentiate this malignancy from the anaplastic and pleomorphic areas of dedifferentiation [55].
- Gastrointestinal mesenchymal tumors with heterologous components must be considered in differential diagnosis of GIST with rhabdomyoblastic differentiation. Malignant peripheral nerve sheath tumor (MPNST) with divergent differentiation (malignant “Triton” tumor) is a rare lesion that can occur sporadically or in association with neurofibromatosis type 1 [56]. Nuclear morphology, biphasic morphological pattern with cellular and hypocellular areas exhibiting a palisading or neuroid whorling pattern, increased cellular density around the blood vessels, and positivity for S-100 protein favor the diagnosis of the malignant Triton tumor [57].
- Dedifferentiated liposarcoma is another distinct entity that can present a potential diagnostic pitfall. Assessment of mouse double minute-2 homolog (MDM2) amplification by fluorescence *in situ* hybridization (FISH) analysis, immunohistochemical staining for MDM2 and CDK4, adequate sampling including fat tissue, and *KIT* mutational analysis are powerful tools to differentiate between the two lesions [58,59].
- Histologically, dedifferentiated areas are adjacent to classical GIST parts, which helps to distinguish them from other entities. However, the diagnosis can be far more challenging if the dedifferentiated component is observed alone (without the conventional GIST component). For example, Antonescu et al. reported the case of an anaplastic tumor, lacking a conventional KIT-positive component, in the small intestine. Molecular analysis demonstrated the presence of a *KIT* exon 11 mutation, which sufficed for GIST diagnosis [16]. In light of the previous findings, tumor dedifferentiation should always be considered in the presence of an undifferentiated or anaplastic sarcoma because GIST is the most common type of sarcoma in the gastrointestinal tract. In these cases, extensive sampling to include a conventional GIST component and mutational analysis are crucial to confirm the diagnosis.

8. Conclusion

Dedifferentiation of GISTs can occur regardless of treatment with imatinib and presents with different morphologies, including rhabdomyosarcoma, angiosarcoma, or undifferentiated pleomorphic sarcoma. To date, most reports have not shown additional mutations in the original driver oncogene. Instead, the tumors exhibited genetic instability, indicated by LOH or low-level KIT amplification. The previous alterations, alongside morphologic and immunophenotypic changes that occur during the dedifferentiation process suggest the possible activation of alternative pathways driven by KIT-independent oncogenic mechanisms. The possibility of dedifferentiation in GISTs should always be considered when an undifferentiated sarcoma component is identified in the gastrointestinal tract.

Declarations of interest

None.

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