haematologica
Journal of the Ferrata Storti Foundation

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Received: May 27, 2026.
Accepted: September 15, 2026.

Citation: Kylie Rose Everard, Mark Anthony Turingan, Ingrid Tam and Ali Sakhdari.
DLBCL2IDCS: transdifferentiation of diffuse large B-cell lymphoma to interdigitating dendritic cell sarcoma.
Haematologica. 2026 Sept 24. doi: 10.3324/haematol.2026.301316 [Epub ahead of print]

DLBCL2IDCS: transdifferentiation of diffuse large B-cell lymphoma to interdigitating dendritic cell sarcoma

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Artificial intelligence / generative AI use disclosure

AI did not make substantive intellectual contributions to the work

Data availability

All data generated or analysed during this study are available upon request.

Author contributions

All authors contributed to data generation, analysis, and manuscript preparation.

Disclosures

The authors have no disclosures to report.

Interdigitating dendritic cell sarcoma (IDCS) is an aggressive malignant neoplasm that recapitulates the morphology and immunophenotype of interdigitating dendritic cells, the antigen-presenting cells resident in the T-cell zones of lymphoid organs.[1,2] IDCS is exceedingly rare, with approximately 200 cases reported in the literature, and carries a median overall survival of 12 months and a disease-specific mortality rate of 36.4%.[3] The diagnosis relies on a characteristic immunophenotype: strong S100 positivity, variable expression of histiocytic markers (CD68, lysozyme), and negativity for CD1a and Langerin, which distinguishes IDCS from Langerhans cell sarcoma.[1,2] Genomic alterations in the MAPK pathway are frequently identified in IDCS and other malignant histiocytic neoplasms.[4,5]

IDCS has been reported in association with other hematologic malignancies of both myeloid and lymphoid origin, with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) being the most common,[6] and Follicular lymphoma (FL) being the second most frequently reported association.[7] When clonality is established between the two neoplasms, the phenomenon is termed transdifferentiation, reflecting lineage plasticity of the neoplastic B-cell clone. [8,9] The 2021 SH/EAHP Workshop reported 29 cases of B-cell lineage neoplasms transdifferentiating into histiocytic/dendritic cell neoplasms (HDCN) and confirmed substantial heterogeneity in the resulting tumors, with IDCS being among the rarest outcomes. [9] Mutations in *MAP2K1* have been specifically implicated in the pathogenesis of transdifferentiation to IDCS.[10]

Here we present a patient who initially presented with diffuse large B-cell lymphoma (DLBCL) with *MYC* and *BCL2* rearrangements and was found to develop clonally related IDCS shortly after achieving remission.

The patient is a 44-year-old male who initially presented in February 2024 with an enlarging left neck mass and tonsillar enlargement. Past medical history was non-contributory. Computed tomography demonstrated enlarged bilateral palatine tonsils and a hypoattenuating lesion with rim enhancement, measuring 4.3 × 3.2 × 2.8 cm, in the left neck. Excisional biopsy performed on the mass revealed diffuse large B-cell lymphoma of germinal center subtype. Flow cytometry was not performed. Fluorescence in situ hybridization (FISH) performed on formalin-fixed paraffin-embedded (FFPE) tissue demonstrated *MYC* and *BCL2* rearrangements (ISCN: nuc ish (BCL6x2) , (MYCx2~3) (5'MYCsep3'MYCx1) [77/200] , (BCL2x2) (3'BCL2 sep5'BCL2x1)[52/200]**),** with *MYC* rearrangement detected in 38.5% (77/200) of nuclei and *BCL2* rearrangement in 26% (52/200) of nuclei, yielding a final diagnosis of DLBCL with *MYC* and *BCL2* rearrangements (Figure 1).

B-cell clonality studies performed on FFPE tissue demonstrated a clonal IGH/IGK gene rearrangement. Next-generation sequencing (NGS) was not performed on the DLBCL specimen, and the tissue was subsequently exhausted, precluding retrospective molecular comparison. The patient completed 6 cycles of R-CHOP, and positron emission tomography (PET) performed in August 2024 revealed no residual disease.

Nine months after the initial DLBCL diagnosis, the patient reported a progressively growing left neck mass at the same site as the previous malignancy. An incisional biopsy was performed; however tissue was not submitted for flow cytometry. Morphologic examination demonstrated nodal architecture effaced by diffuse and nodular aggregates of abnormal large,

oval- to spindle-shaped cells with abundant eosinophilic to finely vacuolated cytoplasm. Nuclei were oval, with occasional indentation and grooves, vesicular chromatin, and distinct nucleoli (Figure 2). Focal necrosis and rare eosinophils were identified.

Immunohistochemical analysis demonstrated a histiocytic/dendritic cell immunophenotype. Lesional cells exhibited diffuse positivity for CD68, CD163, and S100, with co-expression of OCT2 and BCL6, and were negative for CD1a, an immunoprofile consistent with IDCS. B-cell–associated antigens (CD19, CD20, CD79a, and PAX5) and T-cell–associated antigens (CD3) were uniformly negative in the neoplastic population. No residual or admixed B-cell aggregates were identified. Melanoma-associated markers, including HMB-45, SOX10, and Melan-A, were negative in the IDCS specimen. Histochemical stains for infectious organisms, including Ziehl-Neelsen for acid-fast bacilli, Grocott methenamine silver (GMS) for fungi, and immunohistochemistry for *Treponema pallidum*, were all negative (Table 1).

B- and T-cell clonality studies demonstrated a clonal IGH gene rearrangement only. FISH identified BCL2 rearrangement ((BCL2x2) (3'BCL2 sep5'BCL2x1) [66/200]), in 33% of nuclei as well as gains but no rearrangement of *MYC* and *BCL6***.** NGS identified point mutations in *KMT2D* (Variant allele frequency [VAF] 20%), *MAP2K1* (VAF 21%), *CREBBP* (VAF 17%), and *STAT3* (VAF 20%). A diagnosis of interdigitating dendritic cell sarcoma was rendered.

Treatment to date has included 6 cycles of R-CHOP (for the initial diagnosis of double-hit DLBCL), achieving a metabolic complete response. Following new diagnosis of a *MAP2K1*-mutated malignant IDCS, therapy has consisted of: first-line trametinib (requiring dose reduction for rash/folliculitis), second-line gemcitabine/docetaxel, and third-line etoposide/ifosfamide. Palliative radiation has also been delivered to the left tonsil/cervical nodes and to the left pelvis. Most recent restaging demonstrated further progression across nodal, pulmonary, chest wall, soft tissue, and peritoneal sites.

The presence of an identical clonal IGH gene rearrangement in the DLBCL and IDCS, together with a shared *BCL2* rearrangement, provides compelling evidence that the IDCS arose through transdifferentiation from the antecedent DLBCL clone rather than representing a *de novo* second malignancy. Transdifferentiation from B-cell neoplasms to histiocytic/dendritic cell neoplasms (HDCN) is a well-recognized but rare phenomenon, most commonly reported in association with low-grade B-cell lymphomas, particularly CLL/SLL and follicular lymphoma.[6,7,15] DLBCL as a precursor to transdifferentiated HDCN is exceedingly uncommon.[8,16] Our case documents transdifferentiation to IDCS which, to our knowledge, represents the first reported case of DLBCL-to-IDCS transdifferentiation with comprehensive molecular characterization.

The presence of *KMT2D* and *CREBBP* mutations in the IDCS is highly suggestive of a shared clonal origin. *KMT2D* and *CREBBP* are among the most frequently mutated genes in germinal center-derived B-cell lymphomas, representing early founder events in lymphomagenesis.[11] Several studies showed that secondary HDCN associated with antecedent FL frequently shared mutations in *CREBBP* or *KMT2D*.[9,12] The co-occurrence of

BCL2 rearrangement, similar clonal IGH rearrangement, and germinal center-associated epigenetic modifier mutations in our case provides compelling, albeit indirect, evidence for a clonal relationship with the antecedent DLBCL.

The molecular mechanism of transdifferentiation of B-cell to HDCN is thought to involve reprogramming of the transcription factor networks governing lineage identity. Experimental studies have demonstrated that enforced expression of the myeloid transcription factors C/EBPα and C/EBPβ in differentiated B cells leads to rapid reprogramming into macrophages through inhibition of PAX5, downregulation of CD19, and synergy with endogenous PU.1.[13] The HDCN with antecedent B-cell lymphoma consistently show loss of PAX5 expression.[7,8,9] In our case, the IDCS was negative for PAX5, consistent with this paradigm.

IDCS is the rarest subtype of malignant histiocytic neoplasm, and molecular data are extremely sparse. In the largest genomic profiling study of malignant histiocytic/dendritic cell sarcomas, Massoth et al. performed comprehensive genomic profiling on 102 cases, of which only 7 were IDCS. [4] Across all subtypes, *CDKN2A* mutations were most frequent (32%), followed by *TP53* (22%). MAPK pathway mutations were enriched in the malignant histiocytosis group (histiocytic sarcoma, IDCS, and Langerhans cell sarcoma).[4,17] More recently, Ermakov et al. performed whole-exome sequencing on nine primary lung IDCSs and found a heterogeneous genetic landscape with no common driver mutations, though cancer-actionable copy number alterations were identified in almost all tumors.[19] These findings underscore the molecular heterogeneity of IDCS and the critical need for additional molecular data.

Given that in our case the IDCS did not demonstrate *MYC* rearrangement, which was present in the original DLBCL, two possible routes of pathogenesis may be considered. The first is that the IDCS differentiated from a subclone of the DLBCL that had not yet acquired *MYC* rearrangement. The second possibility is that both DLBCL and IDCS developed from an underlying follicular lymphoma precursor harboring the *BCL2* rearrangement and epigenetic modifier mutations, with transformation to DLBCL (acquiring *MYC* rearrangement) and transdifferentiation to IDCS representing two independent evolutionary trajectories from a common ancestor.[8]

HDCN frequently demonstrate activating mutations in the MAPK pathway.[4] Our case revealed a point mutation (c.361T>A) in *MAP2K1*, encoding MEK1. *MAP2K1* mutations have been specifically implicated in the pathogenesis of transdifferentiation to IDCS.[11] The acquisition of a MAPK pathway mutation may represent a critical secondary genetic event that drives the lineage switch, as RAS/MAPK pathway mutations were frequently identified secondary HDCN.[10] Although the *MAP2K1* mutation is a potentially actionable MAPK-pathway alteration, the clinical course in this case—progression on first-line MEK inhibition with trametinib—illustrates that the presence of a *MAP2K1* mutation within a complex, multi-mutation genomic background does not guarantee durable therapeutic benefit. [14]

In conclusion, this case illustrates the rare phenomenon of transdifferentiation from DLBCL to IDCS, supported by shared BCL2 rearrangement, similar clonal IGH gene rearrangement, and the presence of germinal center-associated *KMT2D* and *CREBBP* mutations in the IDCS. Although direct molecular comparison with the original DLBCL was not possible, the constellation of findings provides compelling evidence for a clonal relationship. The acquisition of a *MAP2K1* mutation in the IDCS component implicates MAPK pathway activation as a potential driver of the lineage switch. This case underscores the importance of comprehensive molecular profiling in histiocytic/dendritic cell neoplasms (HDCN) arising in the setting of prior B-cell lymphoma, both to establish clonal relationships and to identify actionable therapeutic targets.

This study was not supported by any funding. The authors declare that they have no conflict of interest.

This retrospective study was approved by the University Health Network Research Ethics Board (REB No. 21.5741) and was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for written informed consent was waived by the Research Ethics Board because of the retrospective nature of the study and the use of archived clinical data and tissue specimens.

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Marker	DLBCL	IDCS	Marker	DLBCL	IDCS	Marker	DLBCL	IDCS
CD20	+	−	CD79a	+	−	CAM5.2	NP	−
CD10	+	−	PAX5	+	−	BRAF V600E	NP	−
BCL6	70%	+	MUM1	−	−	EBER ISH	−	−
MYC	70%	0.2	CD3	−	−	P53	?	Wild-type
OCT2	+	+	CD15	NP	−	Ki-67	60-70	20–30%
CD68	NP	+	CD21	-	−	*BCL2* rearrangement	+	+
CD163	NP	+	CD30	-	−	*MYC* rearrangement	+	− (gains only)
S100	NP	+	CD34	NP	−	*BCL6* rearrangement	−	− (gains only)
CD1a	NP	−	CD56	NP	−	IGH clonality	Clonal	Clonal
CD4	NP	+	CD61	NP	−	TR clonality	NP	Non-clonal
CD14	NP	+	CD117	NP	−	*KMT2D* mutation	NP	+ (VAF: 20%)
CD33	NP	+	MPO	NP	−	*MAP2K1* mutation	NP	+ (VAF: 21%)
CD45	+	+	SOX10	−	−	*CREBBP* mutation	NP	+ (VAF: 17%)
CD19	+	−	AE1/AE3	−	−	*STAT3* mutation	NP	+ (VAF: 20%)
HMB45	NP	−	Melan-A	NP	−			

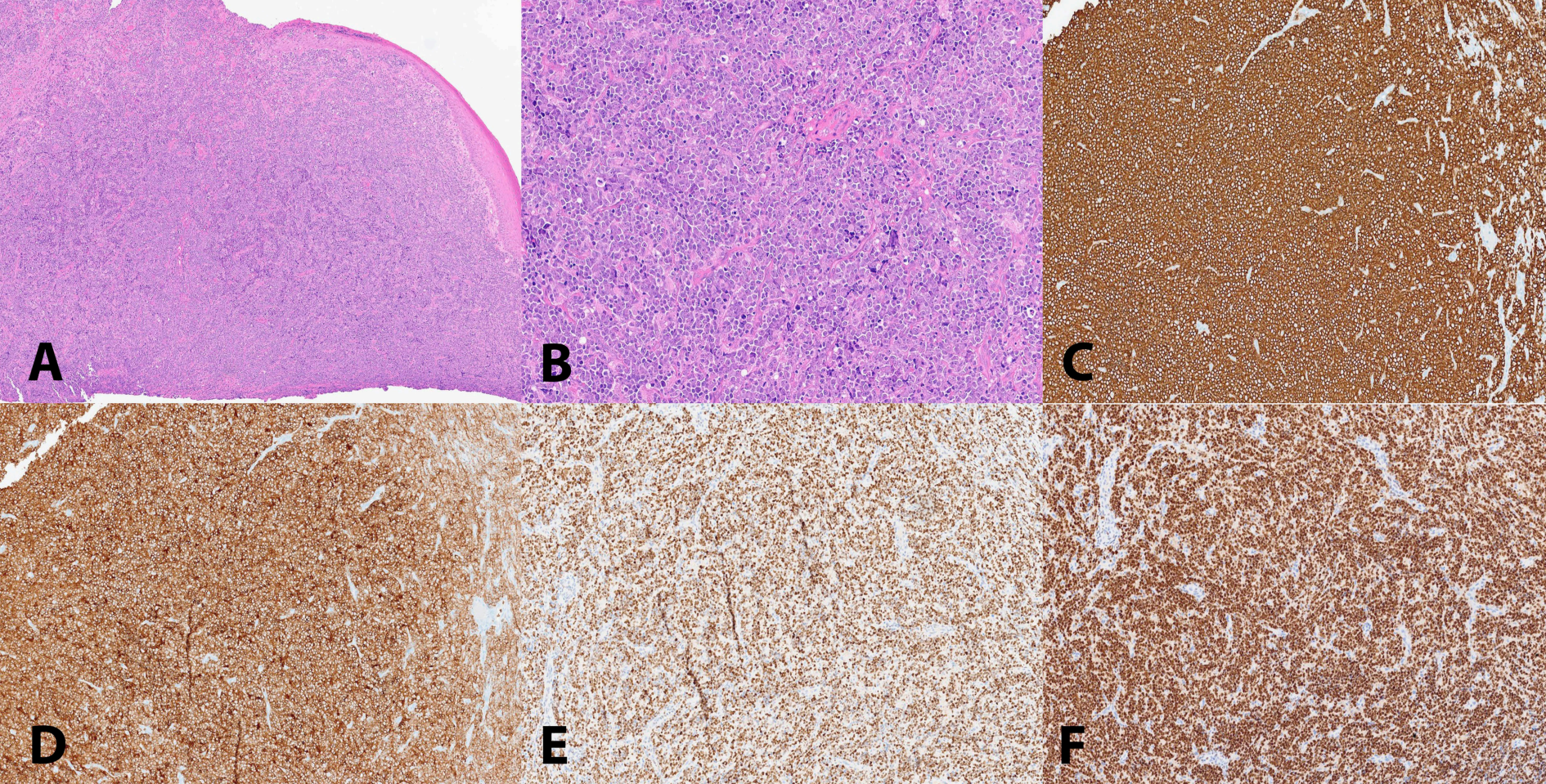
Table 1. Immunophenotypic and molecular comparison of the initial diffuse large B-cell lymphoma and the subsequent interdigitating dendritic cell sarcoma.

Figure 1. Histomorphologic and immunophenotypic features of diffuse large B cell lymphoma.

(A) Hematoxylin and eosin stain, original magnification ×10, showing a diffuse infiltrate effacing nodal architecture. (B) Hematoxylin and eosin stain, original magnification ×40, highlighting sheets of medium to large sized cells with vesicular chromatin and distinct nucleoli and variable amount of pink cytoplasm. (C) CD20, ×10. (D) CD10, ×10. (E) BCL6, ×10. (F) OCT2, ×10. The neoplastic cells show strong positivity for BCL2 and c-Myc (not shown).

Figure 2. Histomorphologic and immunophenotypic features of interdigitating dendritic cell sarcoma.

(A) Hematoxylin and eosin stain, original magnification ×10, showing a diffuse and nodular infiltrate effacing nodal architecture. (B) Hematoxylin and eosin stain, original magnification ×100, highlighting large atypical oval-to-spindled cells with vesicular chromatin and prominent nucleoli. (C) CD68, ×20. (D) CD163, ×20. (E) S100, ×20. (F) CD33, ×20. (G) OCT2, ×20. (H) BCL6, ×20. (I) CD1a, ×20. The neoplastic cells show positivity for histiocytic/dendritic markers and are negative for CD1a, supporting a diagnosis of interdigitating dendritic cell sarcoma.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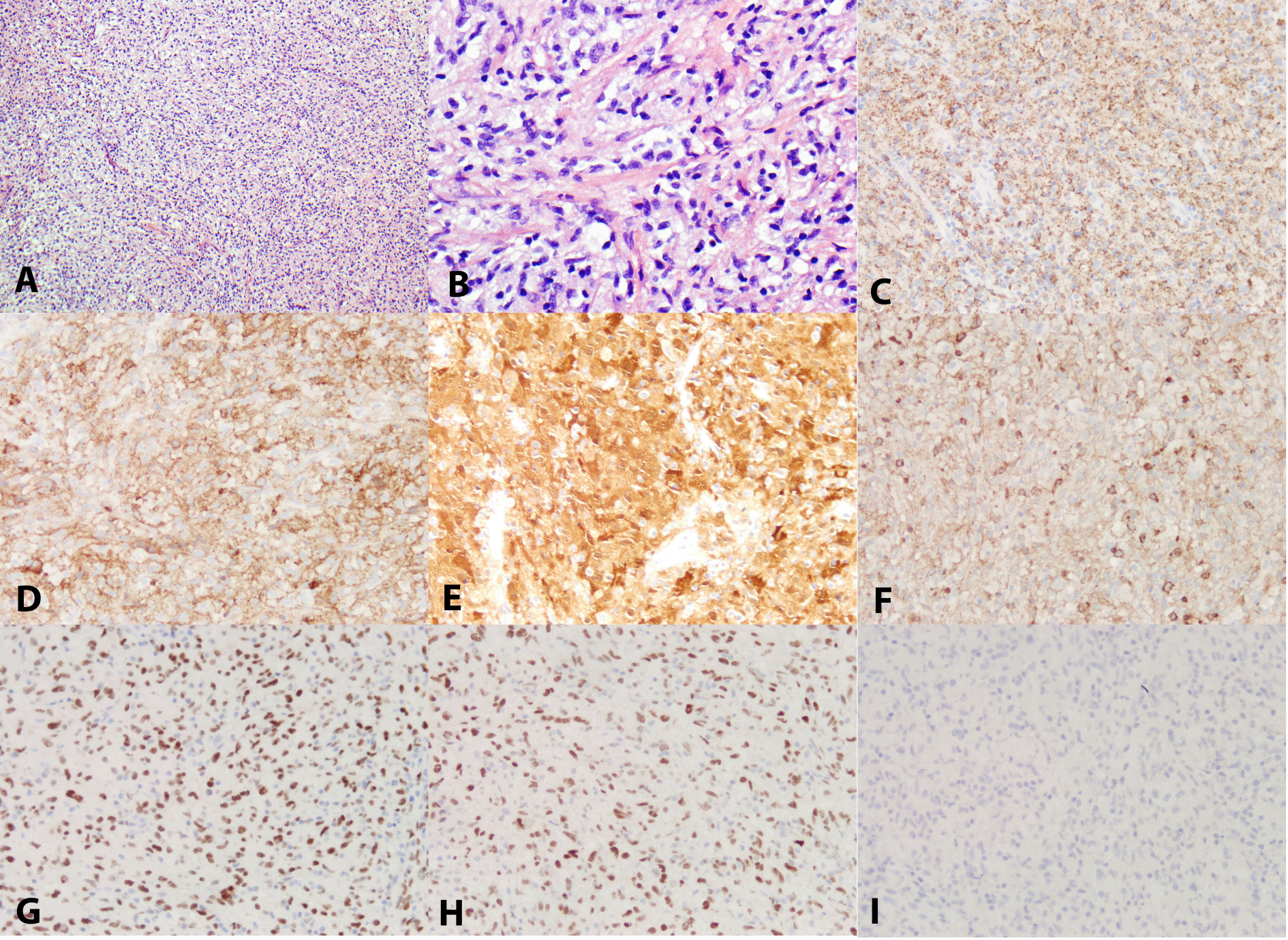
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