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Fetal deaths in Ireland due to SARS-CoV-2 placentitis caused by SARS-CoV-2 Alpha

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ABSTRACT

Context.- A severe third wave of COVID-19 disease affected Ireland in the first 3 months of 2021. In this wave, 1 second trimester miscarriage and 6 stillbirths were observed in the Irish population due to placental insufficiency as a result of SARS-CoV-2 placentitis. This observation was at odds with the country's previous experience with COVID-19 disease in pregnant mothers.

Objective.- To describe the clinical and pathological features of these pregnancy losses.

Design.- Retrospective review of clinical and pathological data of cases of second trimester miscarriage, stillbirth or neonatal death identified by perinatal pathologists as being due to SARS-CoV-2 placentitis during the third wave of COVID-19 in Ireland.

Results.- Clinical and pathological data was available for review in 6 pregnancies. Sequencing or genotyping of the virus identified SARS-CoV-2 Alpha (B.1.1.7) in all cases. Three of the 6 cases had maternal thrombocytopenia, while fetal growth restriction was not prominent suggesting a rapidly progressive placental disease.

Conclusions.- The identification of SARS-CoV-2 Alpha in all these cases suggests that the emergence of the variant was associated with an increased risk of fetal death due to SARS-CoV-2 placentitis when compared to the original virus. Maternal thrombocytopenia, may have potential as a clinical marker of placentitis but other inflammatory markers need investigation. Three of the 6 women had been assessed for reduced fetal movements in hospital some days before the fetal deaths actually occurred; this could suggest that there may be a window for intervention in some cases.

INTRODUCTION

SARS-CoV-2 placentitis represents a readily recognizable pattern of placental injury occurring in some pregnant women who develop COVID-19[1]. Pregnant women are at increased risk of severe COVID-19-associated illness compared with their non-pregnant counterparts, although the absolute and overall risk for severe COVID-19 remains low. This includes an increased risk of intensive care unit (ICU) admission, mechanical ventilation, receiving extracorporeal membrane oxygenation (ECMO) and even death, and after adjusting for age, race/ethnicity and underlying medical conditions [2,3,4,5,6]. Pregnant Black, Asian and Hispanic women have been noted in large studies to have disproportionately higher rates of SARS-CoV-2 infection, ICU admission and death [3]. Pre-existing comorbidities, such as co-existing respiratory and cardiovascular disease, diabetes, advanced maternal age and obesity, seem to be significant risk factors for severe COVID-19 [3,6]. A recent review estimates around a 15% incidence of preterm birth [2]. The most recent United Kingdom (UK) report prepared by the Coronavirus Clinical Characterisation Consortium (ISARIC4C), UK Obstetric Surveillance System (UKOSS) and COVID-19 Clinical Information Network (CO-CIN) for the UK Scientific Advisory Group for Emergencies (SAGE) includes detail on pregnant women with COVID-19 and concluded that of symptomatic pregnant women hospitalized with COVID-19, 10% received critical care and 1% died [7]. In Ireland, the Health Protection Surveillance Centre (HPSC) reported increasing numbers of pregnant or recently pregnant women admitted to critical care in wave 3 and 4 of the pandemic [8,9]. These findings in successive publications and reviews suggest that pregnancy itself may manifest increased complications and morbidities among women with severe and critical COVID-19 symptoms.

One UK single-site study reported early in 2020 that the incidence of stillbirth was significantly higher during the pandemic period than during the pre-pandemic period – however, none of these stillbirths occurred in women positive for COVID-19 [10]. The French

research network also reported a high rate of stillbirths initially; 7 stillbirths among 181 pregnancies between March and April 2020; but with limited detail [11]. However, in subsequent larger series and population-level reports, the risks of stillbirth or neonatal death were not significantly increased [3,4,5,12]. The Centers for Disease Control and Prevention (CDC) Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET) report [4] included 20 stillbirths after 20 weeks from 4,527 infants born to COVID-19 positive mothers, without detailed discussion on cause (0.4%). The updated *British Medical Journal* (BMJ) living systematic review reported 18 stillbirths (27 studies; 2837 offspring) and six neonatal deaths (26 studies; 1728 neonates) that occurred among pregnant and recently pregnant women with COVID-19, resulting in negligible changes in overall risks for perinatal death with COVID-19 [2]. The recent ISARIC/UKOSS/Co-CIN report, comments that due to delays in units notifying stillbirths and neonatal deaths and time lags in receipt of data to allow for cross-checking, Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) 'cannot yet make any confident interpretation of stillbirth and neonatal mortality rates for 2020' [7].

In relation to pathological mechanisms of pregnancy loss, Schwartz et al reported 5 stillborn/terminated infants associated with maternal COVID-19 disease that demonstrate pathological features consistent with SARS-CoV-2 placentitis [13]. Libbrecht et al have also recently reported the loss of a twin pregnancy due to SARS-CoV-2 placentitis [14]. Garrido-Pontnou et al reported 5 pregnancy losses in association with "diffuse trophoblast damage" which would in our opinion be consistent with SARS-CoV-2 placentitis [15]. In other reports of miscarriage or stillbirth in COVID-19 the pathological mechanisms have not been as clear [16-22].

The Republic of Ireland experienced a severe "third wave" of COVID-19 infection from December 2020 through the early months of 2021 (Figure 1A, 1B) with rates of

infection peaking at 529 per 100000 population nationally during week 2 of 2021[23]. This wave was dominated by the Alpha (B.1.1.7) variant of concern [24, 25] which represented 88.7% of sequenced cases through January to March (6765 of 7627 Irish sequences from 01/01/21 to 31/03/21 on the Global Initiative on Sharing All Influenza Data (GISAID) database[26].

Seven cases of fetal death (6 stillbirths and 1 second trimester fetal death) were reported to public health officials in Ireland that were due to SARS-CoV-2 placentitis over the first 3 months of 2021. In all cases the fetal deaths were due to placental insufficiency caused by extensive placental injury. This observation differed from the national experience in 2020 when no fetal deaths were reported.

We sought to describe the clinical and pathological features of cases of second trimester miscarriage, stillbirth or neonatal death identified by perinatal pathologists as being due to SARS-CoV-2 placentitis during the third wave of COVID-19 in Ireland.

MATERIALS AND METHODS

All perinatal pathology units nationally were contacted to identify cases of pregnancy loss due to SARS-CoV-2 placentitis. Pathological features were reviewed between the perinatal pathologists involved. Placentas had been grossly examined after fixation in formalin to reduce the risk of infection. Representative sections of umbilical cord, membranes and parenchyma had been processed to paraffin-embedded blocks with standard hematoxylin and eosin stained slides used for evaluation. Martius Scarlet and Blue (MSB) was used to identify fibrin. Immunohistochemistry protocols varied for the different laboratories involved but for SARS-CoV-2 all laboratories used a spike antibody target (1A9 clone). In the examples used for illustration in this paper immunohistochemistry was performed on 3 μm thick sections using a Ventana BenchMark Ultra with a Ventana Optiview DAB immunohistochemistry (IHC) Detection Kit with Ventana Bluing reagent as a

counter stain. Heat pre-treatment was performed using Ultra Cell Conditioning Solution (Ultra CC1) and Cell Conditioning Solution (Ultra CC2) depending on the monoclonal antibodies tested: CD68 (BOND, RTU, 514H12), CD3 (Ventana, RTU,2GV6), CD20 (Ventana, RTU, L26), CD138 (CellMarque, RTU B-A38), Sars-CoV-2 (Covid-19) Spike Antibody (GeneTex, 1A9, 1:200). For CD61 the antibody was a Roche pre-dilute CD61 (2f2), reference no. V0002430.

SARS-CoV-2 variant identification was performed by the National Virus Reference Laboratory (NVRL) using either whole genome sequencing (WGS), using the ARTIC protocol and nanopore sequencing [27], or by using a real-time reverse transcription-polymerase chain reaction (RT-PCR) assay that specifically targets single nucleotide polymorphisms characteristic of the Alpha (B.1.1.7), or other, e.g. Beta and Gamma, SARS-CoV-2 variants (the ViroBOAR assay, Eurofins Genomics, Germany).

Post mortem records were reviewed and relevant pathological findings extracted and correlated with the placental pathological and clinical features.

Clinical features of interest were extracted from the mothers' medical records.

Appropriate written consent was obtained from the mothers of the infants involved for use of anonymized clinical details and laboratory data for the purposes of publication in medical literature. Ethics approval was obtained from the Royal College of Physicians Ireland (RECSAF 152v2).

RESULTS

Six mothers consented to participation in this study and thus the details of 6 of the 7 cases are presented here.

Pathological Features

Placental Pathology.—All placentas showed extensive gross parenchymal abnormalities with coalescing nodules, streaks and plaques of consolidated pale parenchyma evident on placental cross sections (Figure 2, A and B). These gross features resembled those seen in 'massive perivillous fibrin deposition' [28]. The extent of gross parenchymal involvement exceeded 80-90 % in all cases.

On microscopic evaluation the features evident across the slides were heterogenous but with unifying consistencies in pattern. In all cases there was extensive microscopic involvement correlating with the gross placental appearances. Extensive villous trophoblast necrosis was a key feature and this was associated with accumulation of cellular debris and eosinophilic material in the intervillous space (Figure 3, A and B). This in turn was associated with extensive aggregation of villi with obliteration of the intervillous space. This obliteration of the intervillous space in some cases led to disturbance of intervillous blood flow with focal pooling of intervillous blood (Figure 2, A). The combination of these features led to the tissue consolidation evident grossly. While the gross appearance resembled massive perivillous fibrin(oid) deposition the microscopic appearances differed due to the extensive villous trophoblast injury and accumulation of intervillous inflammatory/cellular debris. The MSB stain also showed that fibrin deposition was variable in its distribution, varying from prominent to inconspicuous (Figure, 4 A and B). A CD61 stain showed that platelets were prominent in the intervillous material (Figure 4, C and D).

Apart from the trophoblast necrosis and its associated consequences another consistent feature was intervillositis. This was present in all cases and was variable in its distribution but more readily identified at the edges of more confluently affected areas. While histiocytes appeared to be the major component of the inflammatory infiltrate (Figure 5, A), in some areas T-lymphocytes and B- lymphocytes were identified (Figure 5, B, C and D).

There was a particular tendency of the histiocytes to target the syncytiotrophoblast on the villous surfaces (Figures 5, A and Figure 6, A, B, C and D). It was noted that the histiocyte 'targeting' of the trophoblast wasn't necessarily related to whether or not that particular area was positive for SARS-CoV-2 by immunohistochemistry (Figure 6, C and D). There was no evidence of widespread ingress of the inflammatory infiltrate into the stroma of the villi. Neutrophils were present in response to cellular necrosis.

One placenta had a thrombus in a large chorionic plate vessel.

Immunohistochemistry for SARS-CoV-2 was positive in a patchy to extensive distribution in the villous trophoblast of all cases (Figure 7A, 7B). This fulfils a key component of the recently proposed standardized definition of placental infection by SARS-CoV-2 [29].

Post Mortem Pathology.—Post mortem examinations were conducted in 5 of the 6 cases with the sixth case receiving an external examination with recording of external parameters. There were 3 male and 3 female infants. From the post mortem assessments all infants were anatomically normal. It was notable that none of the infants showed definitive evidence of growth restriction. Histological examination of fetal organs showed no morphological evidence of organ involvement by the infection.

Virology.—As noted above, all placentas stained positively for SARS-CoV-2 by immunohistochemistry. Nasopharyngeal swabs for SARS-CoV- 2 RNA were positive in all of the mothers. In 4 of the 6 cases these swabs had been positive when the mothers were originally diagnosed with COVID-19 some time prior to the intrauterine fetal deaths. The longest interval between a COVID-19 diagnosis and stillbirth was 21 days. The shortest intervals were in two cases where the mothers were found to be positive for SARS-CoV-2 at the time of diagnosis of the stillbirth.

Typing of the viruses identified that all 6 cases were the Alpha (B.1.1.7) variant of concern. Although the clinical aspects of the 7th case are not described here it was also confirmed as involving the Alpha variant.

Clinical Details

The clinical features of the 6 cases are summarized in the provided table.

Five of the women were regarded as having mild symptoms with only two being briefly admitted to hospital. One of these was for gastrointestinal symptoms of abdominal pain, fever and vomiting; this patient was discharged after 2 days. One mother was admitted for respiratory symptoms of chest pain and shortness of breath. She had a fever and ground glass changes on computerized tomography (CT) scan suggestive of COVID-19 pneumonia. She never required oxygen supplementation and was discharged on day 3.

The interval between the maternal COVID-19 diagnosis and diagnosis of fetal death varied from 0 to 19 days.

Three of the 6 women had been assessed for reduced fetal movements in hospital some days before the fetal deaths actually occurred. Case 2 presented with reduced fetal movements 2 days after her COVID-19 diagnosis with a reassuring clinical assessment. An intrauterine fetal death was diagnosed 16 days later. In case 4 the patient had complained of reduced fetal movements 5 days after her COVID-19 diagnosis; clinical assessment was performed with a reassuring cardiotocograph (CTG) and fetal movements evident. An intrauterine fetal death was diagnosed 3 days later. Case 6 presented 8 days after her COVID-19 diagnosis with reduced fetal movements. Evaluation at this time was reassuring and she declined admission. An intrauterine fetal death was diagnosed 4 days later.

One patient had a transaminitis at the time of presentation with the intrauterine fetal death with an alanine aminotransferase (ALT) level of 174 IU/L.

Of note was the presence of thrombocytopenia in 3 of the 6 cases. Case 4 had platelets of 98 x 10^3/μL 5 days after a COVID-19 diagnosis. When she presented with an intrauterine fetal death at 28weeks 5 days weeks gestation her platelets were 66 x 10^3/μL. One day post-delivery her platelets had recovered somewhat to 136 x 10^3/μL. For case 5 the mother's platelets were 75 x 10^3/μL at the time of diagnosis of intrauterine fetal death, this compared to a value of 286 x 10^3/μL approximately 1 month previously. In case 6 the mother had a platelet level of 92 x 10^3/μL during her admission with respiratory illness but her platelets were normal at 193 x 10^3/μL 12 days later when the intrauterine fetal death was diagnosed.

DISCUSSION

Here we have presented the features of 6 fetal deaths from pregnancies where the mothers recently had COVID-19 disease. In all cases the deaths were due to placental insufficiency as a result of SARS-CoV-2 placentitis, a characteristic pathological lesion that signifies direct placental involvement in maternal COVID-19 infection. To our knowledge, informed by direct contacts with perinatal pathology units nationally, there were no COVID-19-related late miscarriages or stillbirths in the Republic of Ireland in 2020. The emergence of 7 cases (with 6 described here) in a 3 month period in 2021 was clinically notable and of significant concern given that this time period coincided with the spread of the Alpha (B.1.1.7) SARS-CoV-2 variant through the Irish population. The 7 fetal death cases reported nationally all involved the Alpha (B.1.1.7) variant. The timing of these cases and the identification of the Alpha (B.1.1.7) variant in them raises the possibility that COVID-19 caused by the Alpha (B.1.1.7) variant shows an increased tendency to affect the placenta and/or an increased severity of placental involvement when compared to placental involvement seen with the original virus. The identification of this cluster prompted the coroners and pathologists involved to work with obstetric colleagues to raise awareness of

these cases nationally in the interests of public health. As the formal process of case publication can take time, and as clinical need required parties to act expeditiously, this led to rapid presentation and discussion of cases at national webinars which subsequently informed discussion on national clinical guidelines and recommendations concerning vaccination in pregnancy.

The placental histopathology in all cases of fetal death was consistent with SARS-CoV-2 placentitis as described in the literature [1] and was consistent with the proposed standardized definition of placental infection by SARS-CoV-2 [29]. The extensive trophoblast necrosis evident together with positive immunohistochemistry for SARS-CoV-2 suggests a direct viral cytopathic effect of the virus in the placenta related to the presence of ACE2 receptors, necessary for viral cell entry, on the syncytiotrophoblast surface [30]. Histiocytes were however also visible bound to the syncytiotrophoblast (showing degenerative changes) in areas of the placenta that stained negatively for the virus (Figure 6 C and D); this may suggest that immune mediated mechanisms also play a role in placental tissue injury.

Placentas from women known or not known to be COVID-19 positive and that display elements of the features described here need to be evaluated by experienced placental pathologists, ideally with access to methods used for virus confirmation in tissues such as immunohistochemistry or RNA in situ hybridization. This is to ensure that cases of SARS-CoV-2 placentitis are identified and correlated with pregnancy outcomes. This applies to fetal deaths but also to surviving babies where the long term effects of potentially significant placental injury need to be evaluated.

Clinical Recommendations

At a minimum a pregnant woman should inform her obstetric care provider if she receives a COVID-19 diagnosis. She should be carefully counseled with regards to having a low threshold for contacting her caregivers should she have a concern with regard to fetal

movements. Based on this limited series of cases, if she does experience reduced movements in the 3 weeks after a COVID-19 diagnosis careful evaluation is necessary. Three of the women presented here reported reduced movements in the period prior to the intrauterine fetal deaths and all 3 had been evaluated in a hospital setting with essentially reassuring findings. This happened before clinicians were aware that SARS-CoV-2 placentitis existed and could present in this manner and highlights the potential difficulty in detecting the condition with standard assessment protocols. A low threshold for admission and monitoring is required in these scenarios. SARS-CoV-2 placentitis resulting in stillbirth appears to be a rapidly evolving inflammatory and destructive process, with all cases here presenting within 21 days of COVID-19 diagnosis.

Fetal growth restriction was not a feature in these cases, possibly due to the rapid course of the condition. It is not known whether umbilical artery Doppler abnormalities preceded the stillbirths, and the liquor volume was reportedly normal in all cases. Based on these observations it is unlikely that ultrasound will be useful in detection or prediction of adverse outcome, as these changes are usually found in more chronic forms of uteroplacental insufficiency. It is likely that fetal movement awareness with cardiotocograph (CTG) surveillance is the optimum form of monitoring, and this should inform clinical assessment.

The women reported here mostly had mild symptoms of COVID-19 with only one requiring brief admission for respiratory symptoms and another a brief admission for gastrointestinal symptoms. Therefore a marker is needed need to help identify pregnant women who are at risk of this placental condition. It is notable that 3 of the 6 cases presented had thrombocytopenia; together with the presence of large numbers of platelets in the intervillous space of the affected placentas this may suggest a form of thrombotic thrombocytopenia with a consumptive focus in the placental parenchyma. The presence of thrombocytopenia may depend on the stage of the illness at which time blood sampling

occurs but it is a feature worthy of further study. When these women presented with pregnancy losses they were managed along routine care pathways with understandably relatively little attention paid to the possibility that the deaths may have been COVID-19 related until the results of placental examinations came to light. For that reason, inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) that would be usually assessed in patients with significant respiratory COVID-19 illness were not necessarily analyzed. Pregnant women presenting with reduced fetal movements or fetal deaths on a background of a COVID-19 diagnosis should have an extensive inflammatory marker panel performed in an attempt to identify a marker that would point to a risk of SARS-CoV-2 placentitis.

CONCLUSIONS

In the 6 pregnancy losses described here, SARS-CoV-2 Alpha has been associated with fetal deaths in a manner not seen in Ireland before the variant entered the population; this suggests to us a change in clinical manifestations of the virus with an increased risk of placental infection and severe injury over the original virus. SARS-CoV-2 placentitis remains an uncommon consequence of maternal COVID-19 infection but continued awareness of the possibility of changes in its frequency and clinical features is required as new SARS-CoV-2 variants emerge.

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FIGURE LEGENDS

Figure 1 - Health Protection Surveillance Centre (HPSC) data:

(A) Shows the number and cumulative number of confirmed COVID-19 cases notified in Ireland by notification date. The severe 3rd peak of infections is clearly visible from January through March. (B) Shows whole genome sequencing results and percentage of sequenced specimens that were found to be the B.1.1.7 (Alpha) variant of concern with specimen collection dates from week 51, 2020 (December 13th 2020) to week 37, 2021 (Sept 18th 2021). The January to March window is dominated by SARS-CoV-2 Alpha. Graphs provided by and reproduced with permission from the Irish Health Protection Surveillance Centre (www.hpsc.ie).

Figure 2 - Gross placental findings:

In (A) the near 100% extent of parenchymal involvement is appreciable with an area of blood pooling indicated by the arrow. In (B) another example has small nodules (arrow) that coalesce to form extensive areas of parenchymal consolidation resembling ‘massive perivillous fibrin(oid) deposition’.

Figure 3 - Trophoblast necrosis:

In (A) a low power view shows an extensive area of villi all showing necrosis of villous trophoblast; this is accompanied by accumulation of necroinflammatory debris in the intervillous space (hematoxylin and eosin stain [H&E] 16x). (B) shows a high power view of necrotic changes in villous trophoblast (arrowheads) with loss of continuity in the trophoblast layer (arrows); there is also collapse of the intervillous space with accumulation of cellular debris (H&E 400x).

Figure 4 - Intervillous space:

MSB stains show variable accumulation of fibrin in the intervillous space with little or no fibrin seen in (A) and plentiful orange/red fibrin in (B) (MSB 100x). In (C) extensive deposition of eosinophilic material and necroinflammatory debris is evident (hematoxylin and eosin stain 200x). (D) shows immunohistochemistry for CD61 which shows extensive deposition of platelets in the intervillous space (200x).

Figure 5 - Intervillositis 1:

In (A) immunohistochemistry for CD68 highlights histiocytes in the intervillous inflammatory infiltrate (200x). In (B) although histiocytes are prominent the intervillous infiltrate is mixed in its composition (hematoxylin and eosin stain 400x). In (C) a CD3 immunostain highlights numerous T-lymphocytes in some areas (200x) while in (D) a CD20 immunostain highlights numerous B-lymphocytes (200x).

Figure 6 - Intervillositis 2:

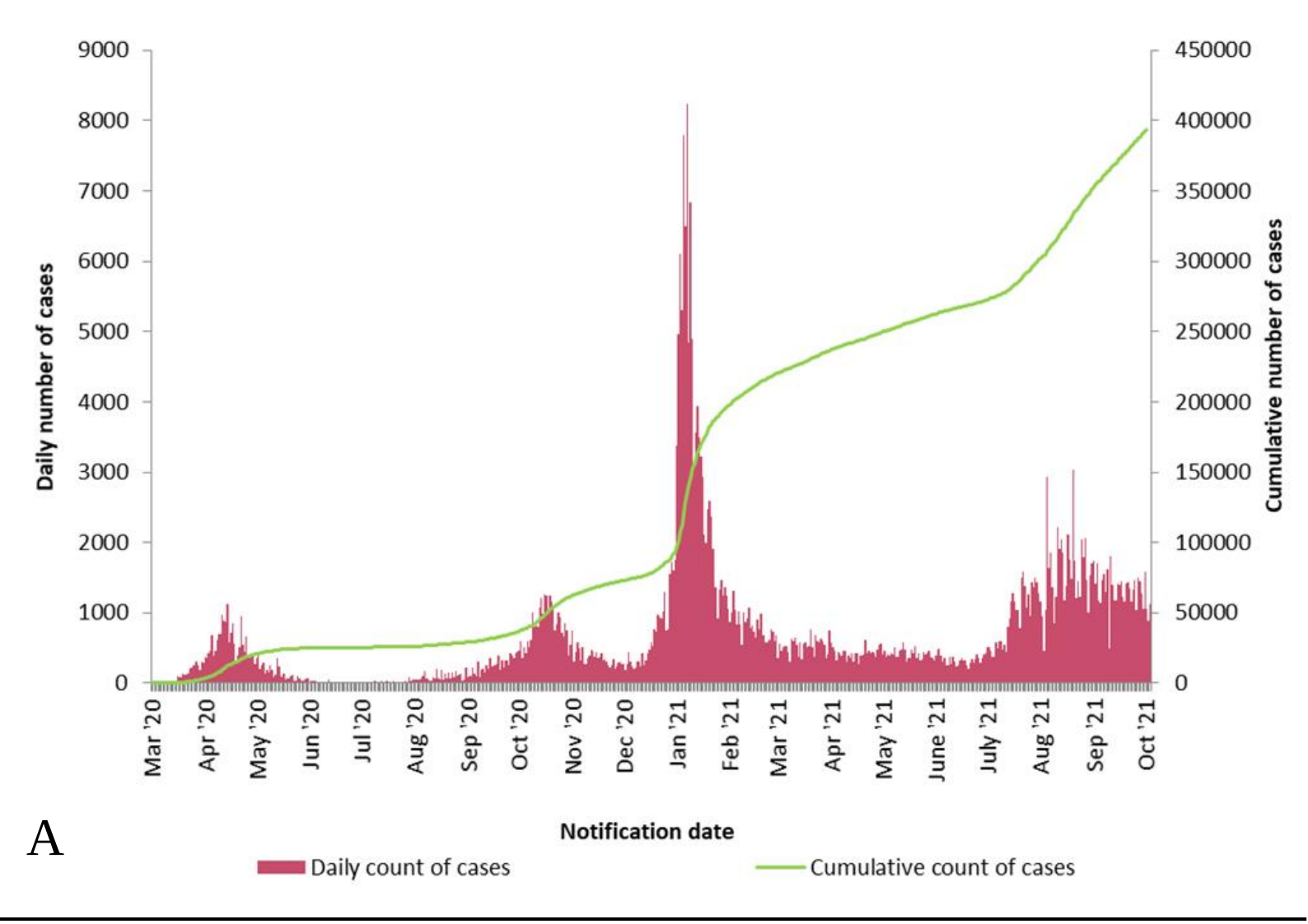
In (A) a prominent intervillositis is present in this medium power view (hematoxylin and eosin stain [H&E] 200x). In (B) the intervillous infiltrate is histiocyte rich with a clear tendency for the histiocytes to adhere to the surface of the syncytiotrophoblast of the small villus in this view (arrow) (H&E 400x). In (C) a villus shows degenerating trophoblast with histiocytes coating its surface (arrows) (H&E 200x). In (D) immunohistochemistry for SARS-CoV-2 shows an absence of staining for the virus in the same villus indicating that in this focus the trophoblast injury may be immune mediated rather than due to viral cytopathic changes (Antibody to SARS-CoV-2 spike protein 200x).

Figure 7 - Immunohistochemistry for SARS-COV-2:

In (A) a low power view shows patchy positive staining for SARS-CoV-2 (arrows) (Antibody to SARS-CoV-2 spike protein 16x). In (B) a higher power view shows clear strong positive staining in villous trophoblast with an absence of staining in the villous stroma (Antibody to SARS-CoV-2 spike protein 200x).

Table: Clinical Detail Summary						
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
Maternal Age	35	28	28	30	26	36
Parity	6	1	1	0	0	3
Body Mass Index	Unavailable	28.7	28	22.6	Unavailable	34.2
Past medical history	Substance abuse	Pancreatitis and cholecystectomy	Splenectomy	None	None	None
Maternal COVID-19 symptoms	None	Mild (vomiting, abdominal pain, fever)	Mild	Mild (fever, abdominal pain).	Mild (cough)	Mild-moderate (fever, ground glass changes on CT, 3 day hospital admission)
Antenatal case	None	Yes	Yes	Yes	Yes	Yes
Thrombocytopenia	No	No	No	Yes	Yes	Yes
Transaminitis	No	No	Yes	No	No	No
Gestational age at maternal COVID-19 diagnosis	24 weeks 3 days	31 weeks	18 weeks 4 days	27 weeks 4 days	30 weeks 1 day	31 weeks
Month of COVID-19 diagnosis in 2021	January	January	March	January	February	March
History of evaluation for reduced fetal movements prior to fetal death occurring	No	Yes	No	Yes	No	Yes
Pregnancy outcome	Spontaneous delivery of stillborn infant at 24 weeks 3 days	Intrauterine death diagnosed at 33 weeks 5 days with induced delivery.	Intrauterine death diagnosed at 20 weeks 3 days with spontaneous delivery.	Intrauterine death diagnosed at 28 weeks 5 days with induced delivery.	Intrauterine death diagnosed at 30 weeks 1 day with induced delivery.	Intrauterine death diagnosed at 32 weeks 5 days with induced delivery.
Fetal weight	550g	1800g	210.3g	1280g	1800g	1960g
Fetal sex	Female	Female	Male	Female	Male	Male

CT indicates computerized tomography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100000
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Cumulative number of cases
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Apr '20
May '20
Jun '20
Jul '20
Aug '20
Sep '20
Oct '20
Nov '20
Dec '20
Jan '21
Feb '21
Mar '21
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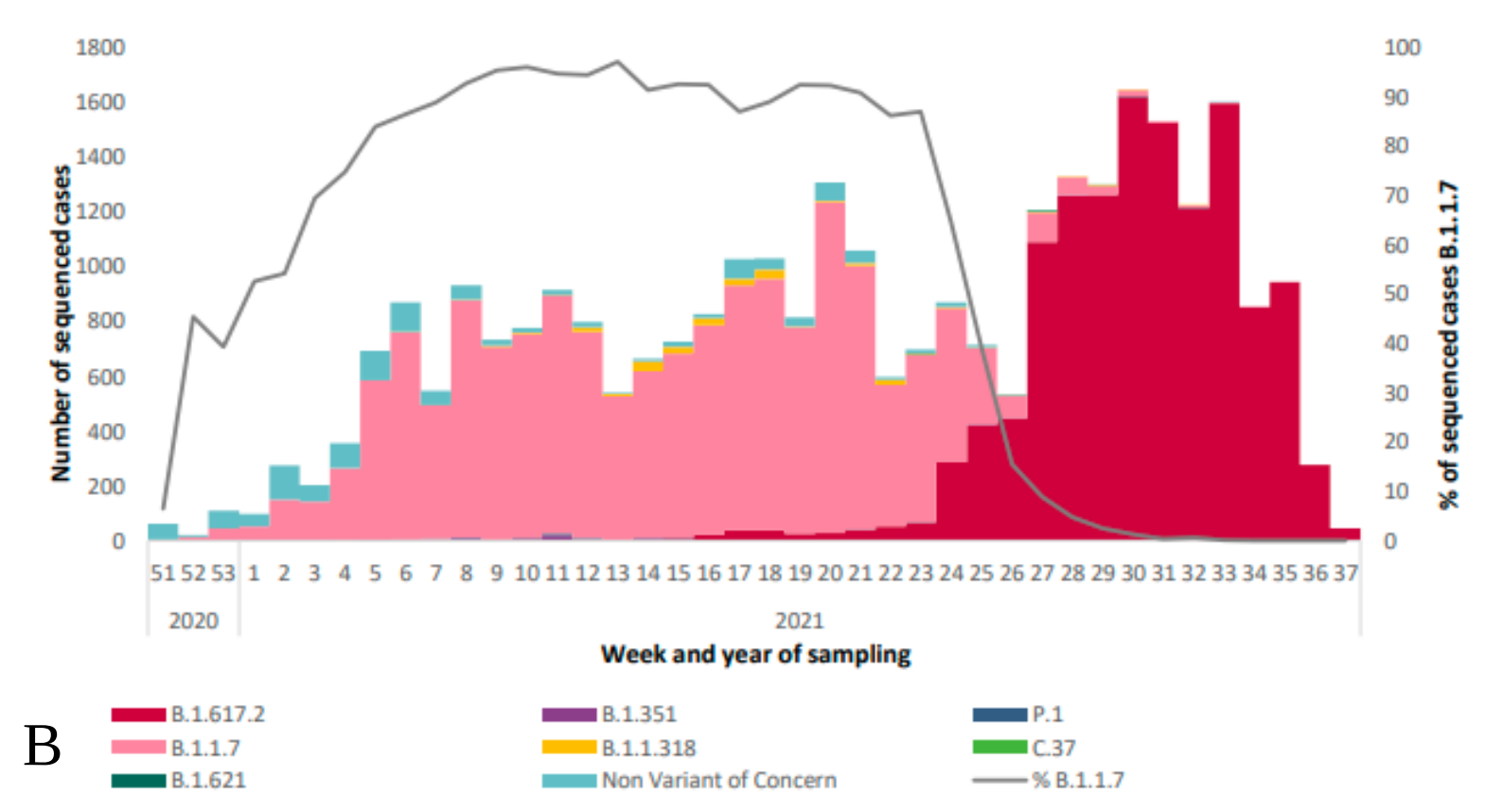
Sep '21
Oct '21
Notification date
Daily count of cases
Cumulative count of cases

A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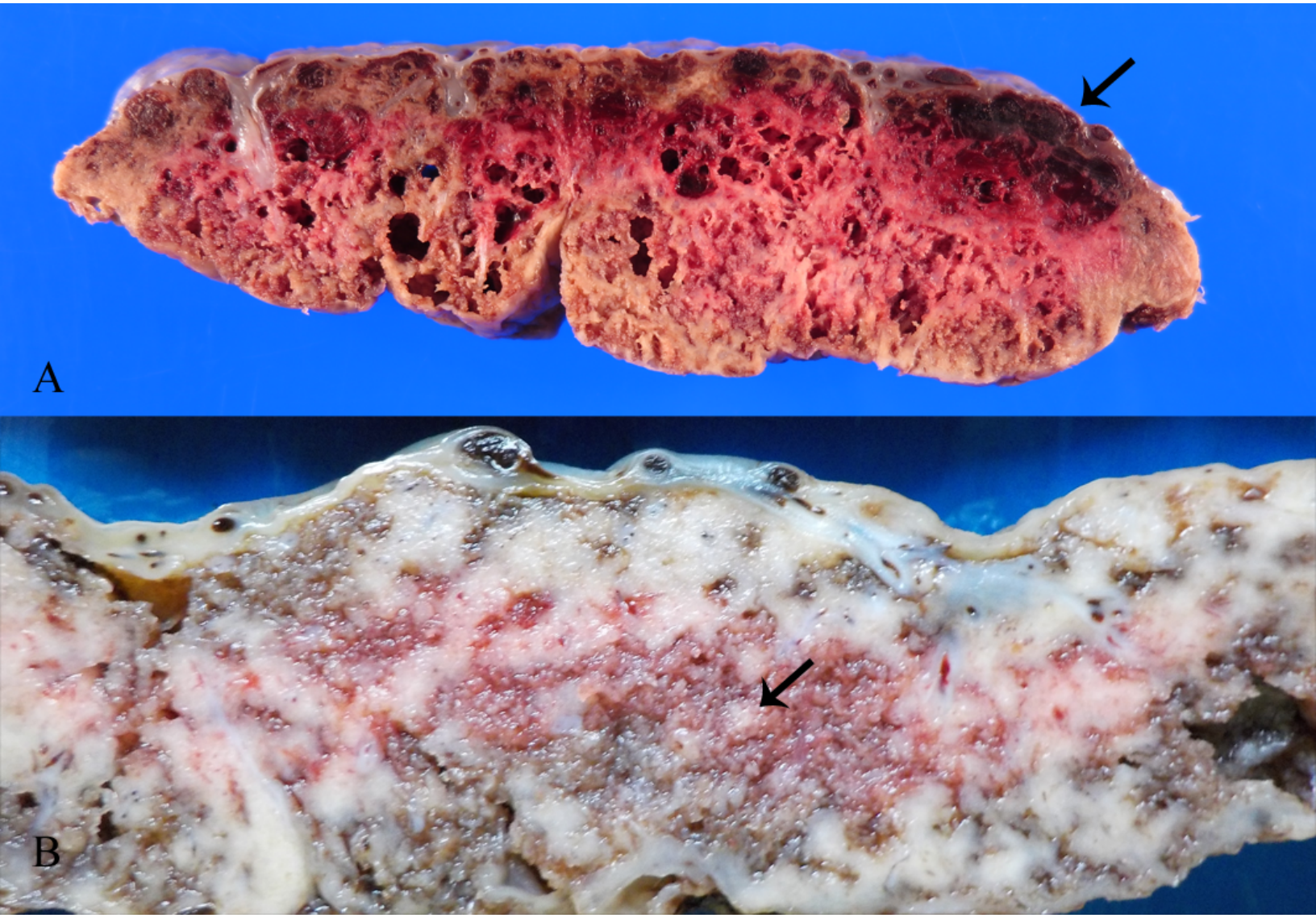
90
80
70
60
50
40
30
20
10
0
% of sequenced cases B.1.1.7
51 52 53 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
2020
2021
Week and year of sampling
B.1.617.2
B.1.1.7
B.1.621
B.1.351
B.1.1.318
Non Variant of Concern
P.1
C.37
% B.1.1.7

B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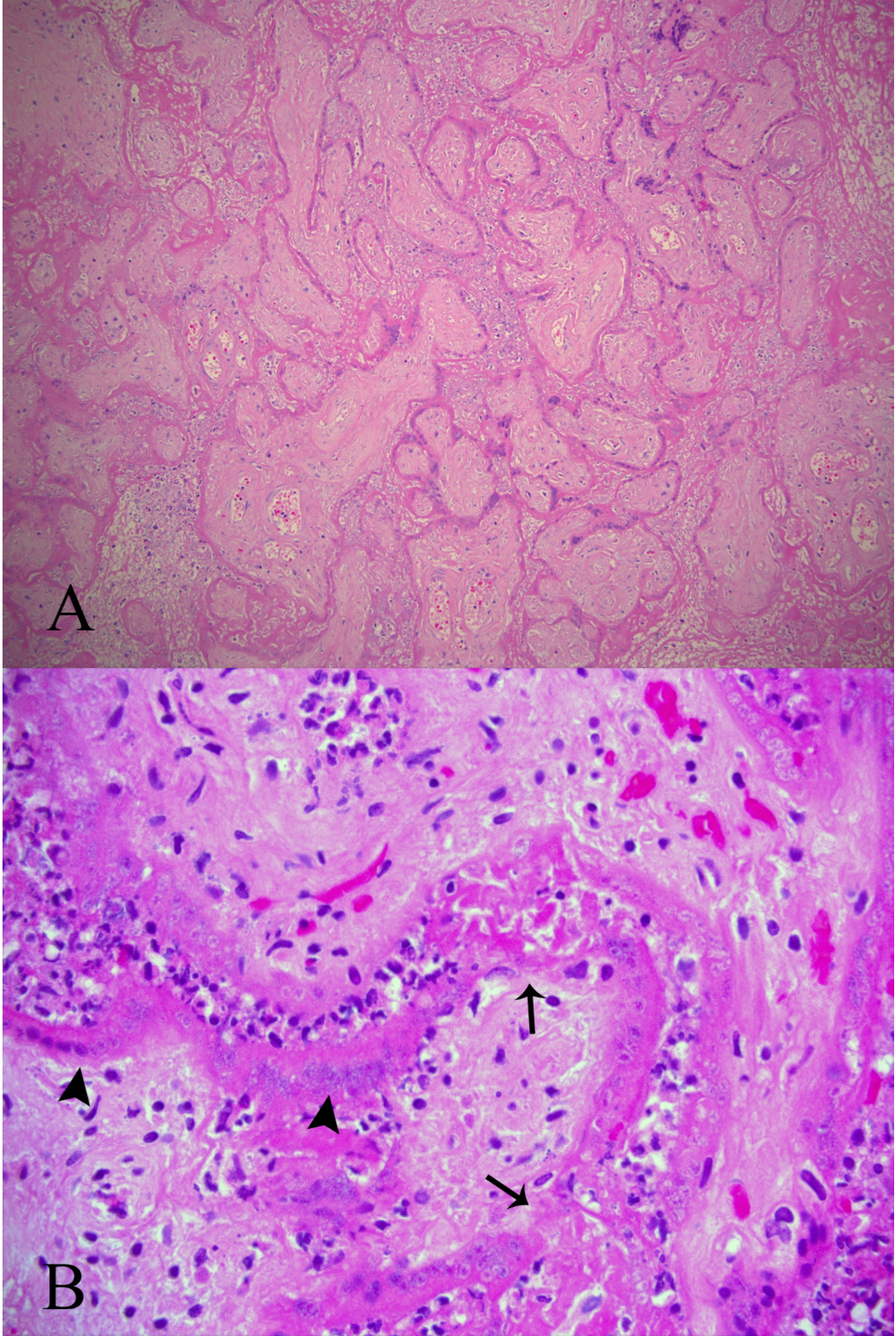
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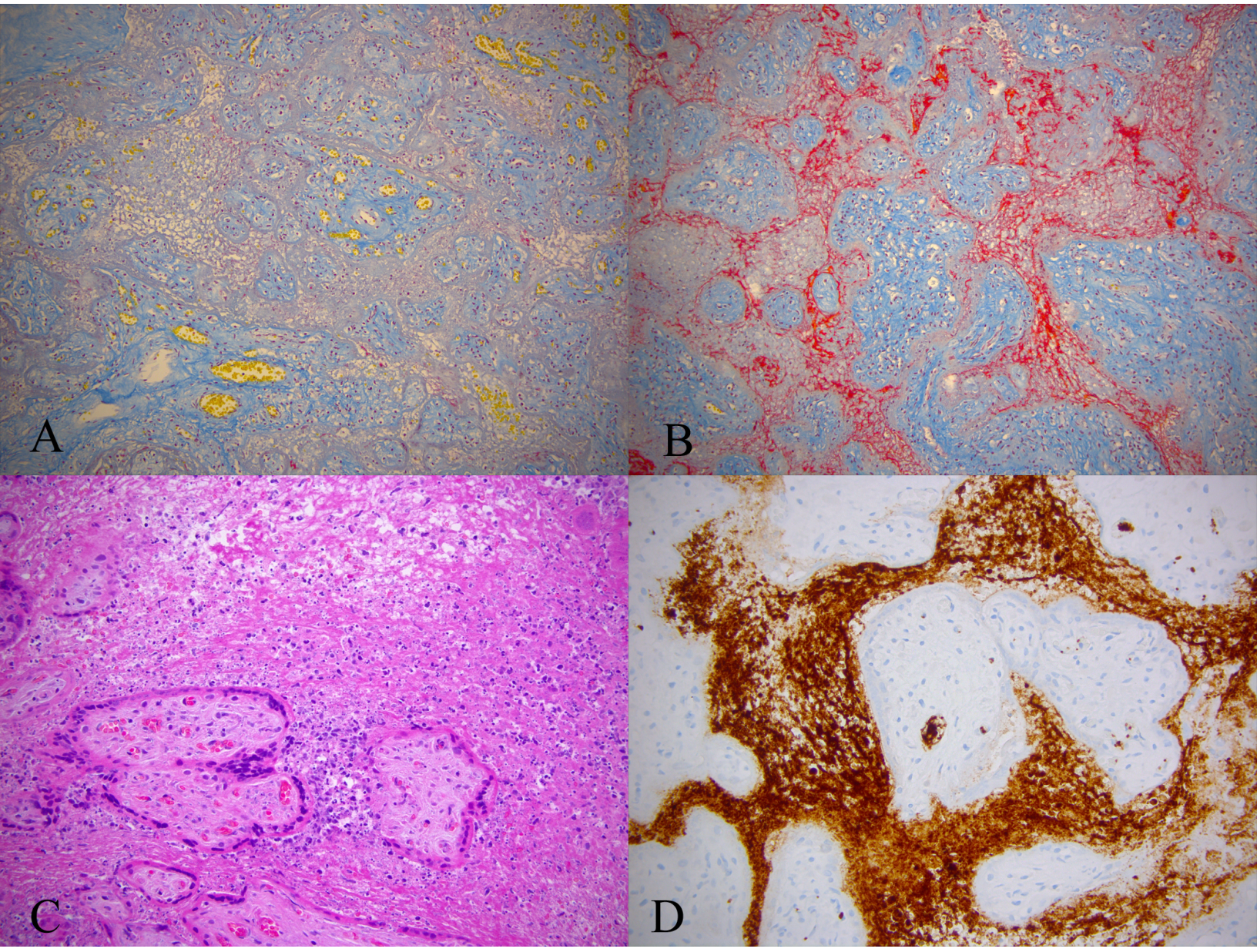
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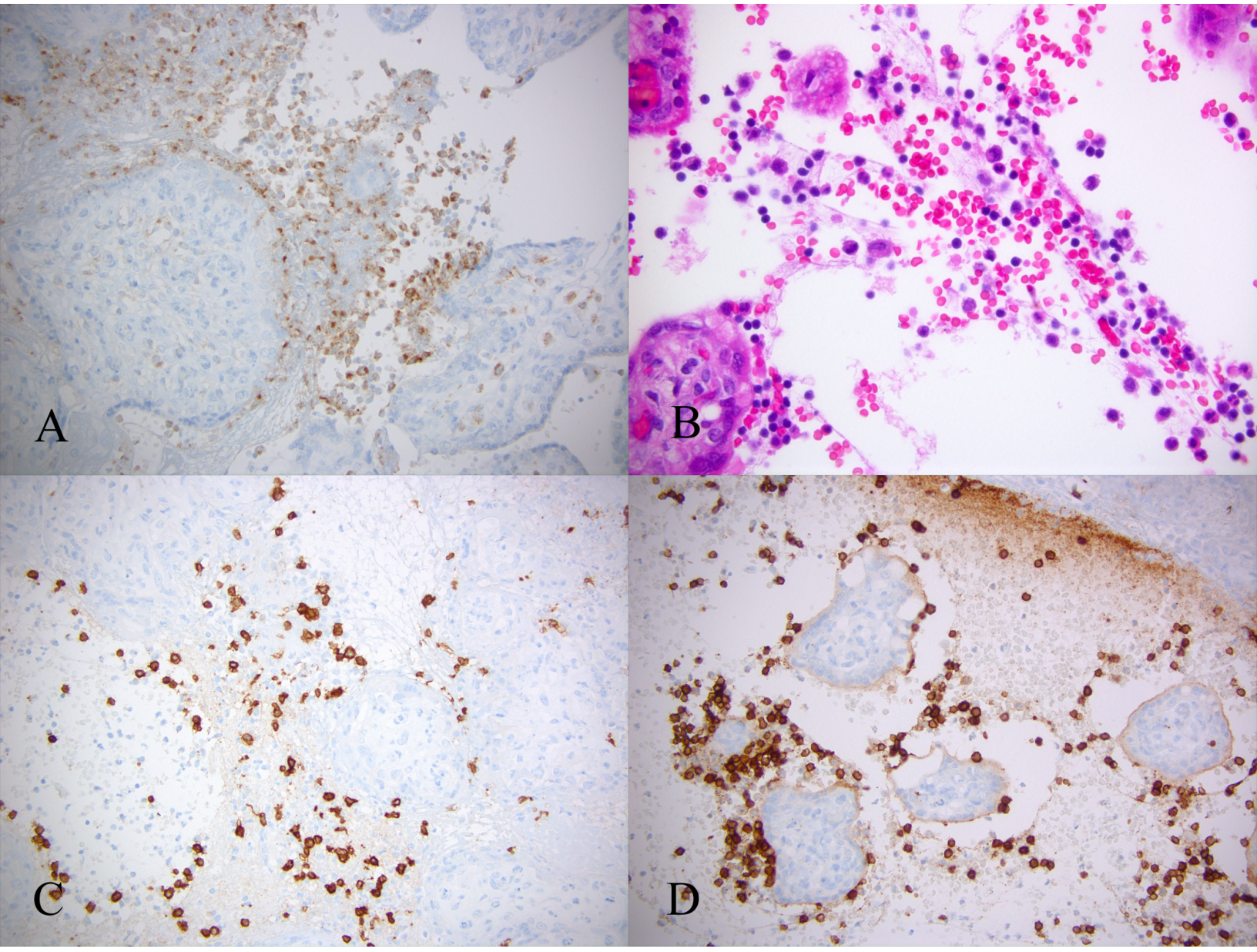
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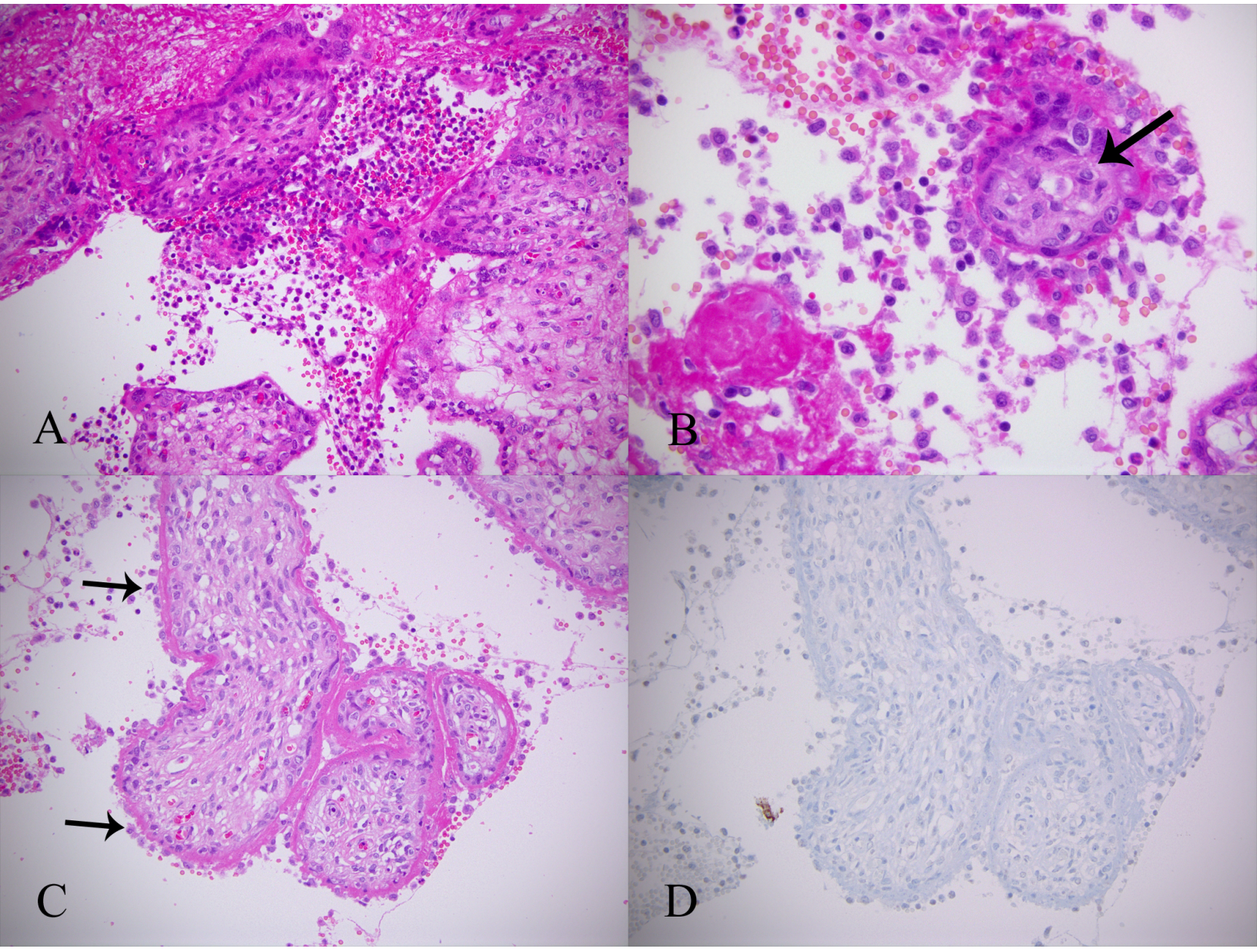
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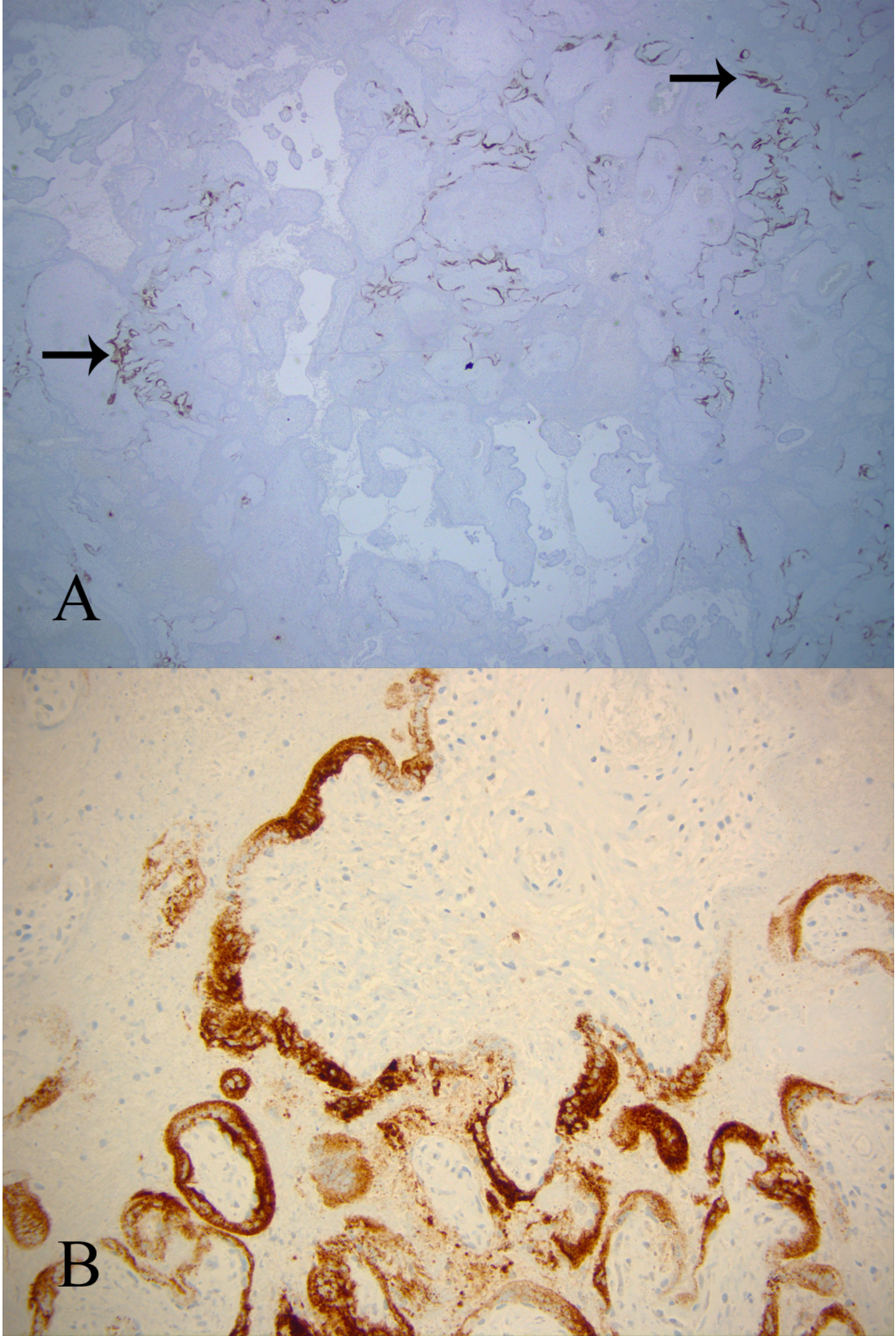
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