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An unusual cause of ascites

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Question:

A 73-year-old man with a past medical history of obesity, diabetes mellitus, alcohol abuse, high blood pressure, and stage 4 chronic kidney disease (due to a diminished vascular system based on kidney biopsy results); presented with severe anemia and major ascites. Physical examination showed an increased abdominal size, and limb edema.

Routine blood tests revealed a hemoglobin of 7 g/dL [13.5; 16.9], reticulocytes 52 G/L, creatinine level at 336 µg/mL [64; 104], alkaline phosphates 240 U/L [38; 126], and gamma glutamyl transferase 236 U/L [15; 73]. Folic acid and B12 vitamin levels were decreased, 1.7 µg/L [3.5; 20.5] and 177 ng/L [187; 883], respectively. Serum protein electrophoresis curve was normal with low albumin level at 33 g/L [40.2; 47.6] and low gamma globulin level at 6g/L [8; 13.5]. HIV, HBV and HCV serology were all negative and there was no biological cause for autoimmune hepatitis.

Abdominal ultrasound showed a dysmorphic hyperechoic fatty liver. The thoraco-abdominal CT scan revealed a dysmorphic liver with irregular shape and cirrhotic morphology, and moderate intraperitoneal effusions in the perihepatic, perisplenic and pelvic space (Figure A). Abdominal paracentesis removed 3L of sterile ascites with a total white blood cell count of 110/mm³ with a vast majority of lymphocytes (71%). Ascites total protein level was at 27 g/L. Serum ascites albumin gradient was not performed. Histologic review of the ascites fluid samples showed lymphocytes associated with benign reactive mesothelial cells. Supplementation with folic acid and B12 vitamin was initiated. Esophageal-gastro-duodenal endoscopy showed stage II esophageal varices, and portal hypertension gastropathy with large gastric folds (Figure B). Gastric biopsy was normal. Liver MRI showed no sign of hepatocellular carcinoma but reveal cirrhotic liver dysmorphia with decompensated portal hypertension (Figure C). A restricted salt diet, and diuretic treatment with aldosterone antagonist were introduced to reduce ascites. Repeated endoscopic variceal ligations were performed, and vaccinations against B hepatitis, hepatitis A and pneumococcal infection were administered to avoid worsening of hepatic disease.

A diagnosis of Child-B cirrhosis with dual etiology of alcoholism and non-alcoholic steatosis hepatitis (NASH) syndrome was made. Hepatic biopsy was not performed.

Six months later, during a regular follow-up consultation, a new paracentesis was performed, with removal of 1.2L of ascites fluid. Despite vitamin supplementation, blood test revealed a recurrence of aplastic anemia with a hemoglobin of 8 g/dL. Ascites total protein was at 31 g/L. Ascites fluid showed a total white blood cell count of 261 cells/mm³ with a majority of histiocytes (52%) associated with numerous Auer-rod-like intracytoplasmic crystal inclusions (Figure D; stain: May-Grünwald Giemsa staining; original magnification x 1000).

In retrospect, the initial paracentesis was reexamined and revealed the presence of crystal inclusions, which had been overlooked by the cytologist previously.

Would you reconsider the initial diagnosis?

Answer :**Establishing the diagnosis:**

Accumulation of crystalline material within the cytoplasm of histiocytes is a very unusual presentation and was never seen before in our laboratory. After a review of the literature we learned that such presentation, known as crystal storing histiocytosis (CSH), is primarily due to the expression of monoclonal immunoglobulins, with plasma cell and lymphoproliferative disorders entities on top of the list¹. As such, cytologists performed a free light chain dosage and lymphocytes immunophenotyping as they are simple routine exams covering 90% of CSH etiologies¹. The results demonstrated an absence of lymphoproliferative disorder but an increase of free light kappa chain at 4.35 g/L with a Kappa/Lambda ratio of 141. According to new criteria established by the International Myeloma Group, a serum involved / uninvolved free light chain ratio of 100 or greater confirms the diagnosis of myeloma.

Review:

Crystal-storing histiocytosis is a rare condition, characterized by intracytoplasmic crystalline inclusion within histiocytes which accumulate, causing multiple organ deficiency. In most cases inclusions are made of monoclonal immunoglobulin deposits¹⁻². CSH is most commonly associated with multiple myeloma and lymphoproliferative disorder with plasmacytic differentiation. Not all cases are associated with neoplastic disease and a very few cases occur in benign disorders such as allergic-autoimmune diseases, inflammatory disorder or even drug induced (typically by Clofazimine) disorders. Treatment depends primarily on the underlying cause.

Pathologists should be aware of this disease, as CSH can be the sign of a more serious condition³. Obvious etiologies for hepatic failure and cirrhosis such as alcohol abuse and NASH syndrome should always be reconsidered when associated with an atypical presentation to prevent misclassification and a delay in diagnosis.

Patient outcome:

A bone marrow aspirate was performed and revealed an intramedullary plasmocytosis at 12% with dystrophic morphology, confirming the myeloma diagnosis. Plasmocytes contained a surprisingly large amount of intracytoplasmic rectangular crystalline inclusions not identified by MGG staining. Crystalline inclusions with the plasma cell did not match the Auer Rod-like inclusions found in the paracentesis histiocytes, and appeared to accumulate over time with cell maturation, resulting in cell lysis by cytoplasmic rupture (Figure E; stain : May-Grünwald Giemsa staining; original magnification x 1000). Needle-like crystalline inclusions identified by MGG staining were observed in bone marrow histiocytes, similar to those observed in ascites fluids (Figure F; stain: May-Grünwald Giemsa staining; original magnification x 1000). It is likely that due to differences in physicochemical properties between plasma cells and histiocytes, the abnormal proteins exhibit different shapes during crystallization.

A Bence-Jones proteinuria was observed with free kappa light chains. Kidney biopsy was performed and showed five myeloma tubes with monotypic kappa expression (Figure G; Kappa immunohistochemistry). No glomerular, interstitial or vascular amyloid deposits were identified with Congo red staining, which would not favor a diagnosis of amyloidosis AL.

The final diagnosis was chronic hepatic and renal failure by accumulation of crystalline inclusion due to an underlying myeloma.

Treatment was initiated with two cycles of daratumumab, dexamethasone, and bortezomib proteasome inhibitor. Treatment efficacy was demonstrated by the decrease of free light chains rate (from 4.35 g/L to 0.032 g/L), normalization of transaminases and improvement of renal function (CKD EPI DFG from 15 to 25 mL/min/1.73m²). No further paracentesis has been required.

References

¹ Mobarki M, Papoudou-Bai A, Dumollard J M, Alhazmi AH, Musawi S, Madkhali MA, Muqri KY, Péoc'h M, Karpathiou G.

Crystal-Storing Histiocytosis: The Iceberg of More Serious Conditions.
Diagnostics (Basel). (2023), 10.3390/diagnostics13020271.

² Dogan S, Barnes L, Cruz-Vetrano WP.

Crystal-storing histiocytosis: report of a case, review of the literature (80 cases) and a proposed classification.

Head Neck Pathol (2012), 10.1007/s12105-011-0326-3.

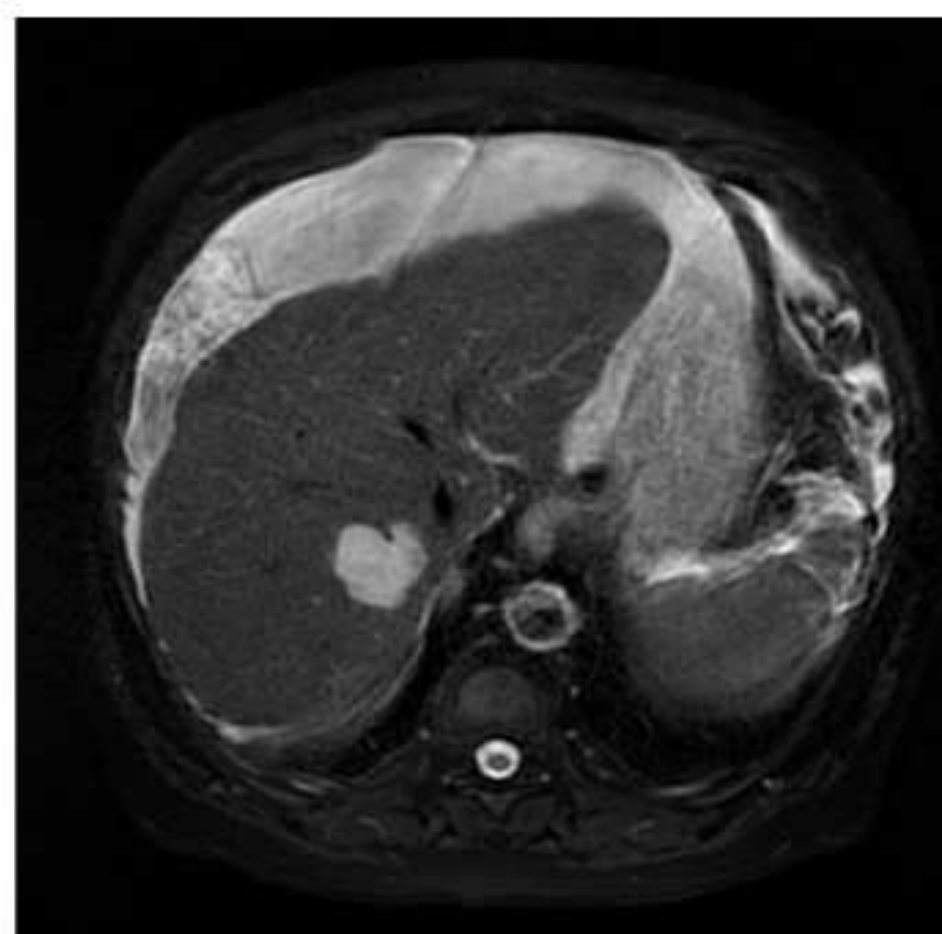
³ Kanagal-Shamanna R, Xu-Monette ZY, Miranda RN, Dogan A, Zou D, Luthra R, Weber DM, O'Malley DP, Jorgensen J L, Khoury J D, Bueso-Ramos CE, Orlowski RZ, Medeiros LJ, Young KH.

Crystal-storing histiocytosis: a clinicopathological study of 13 cases.

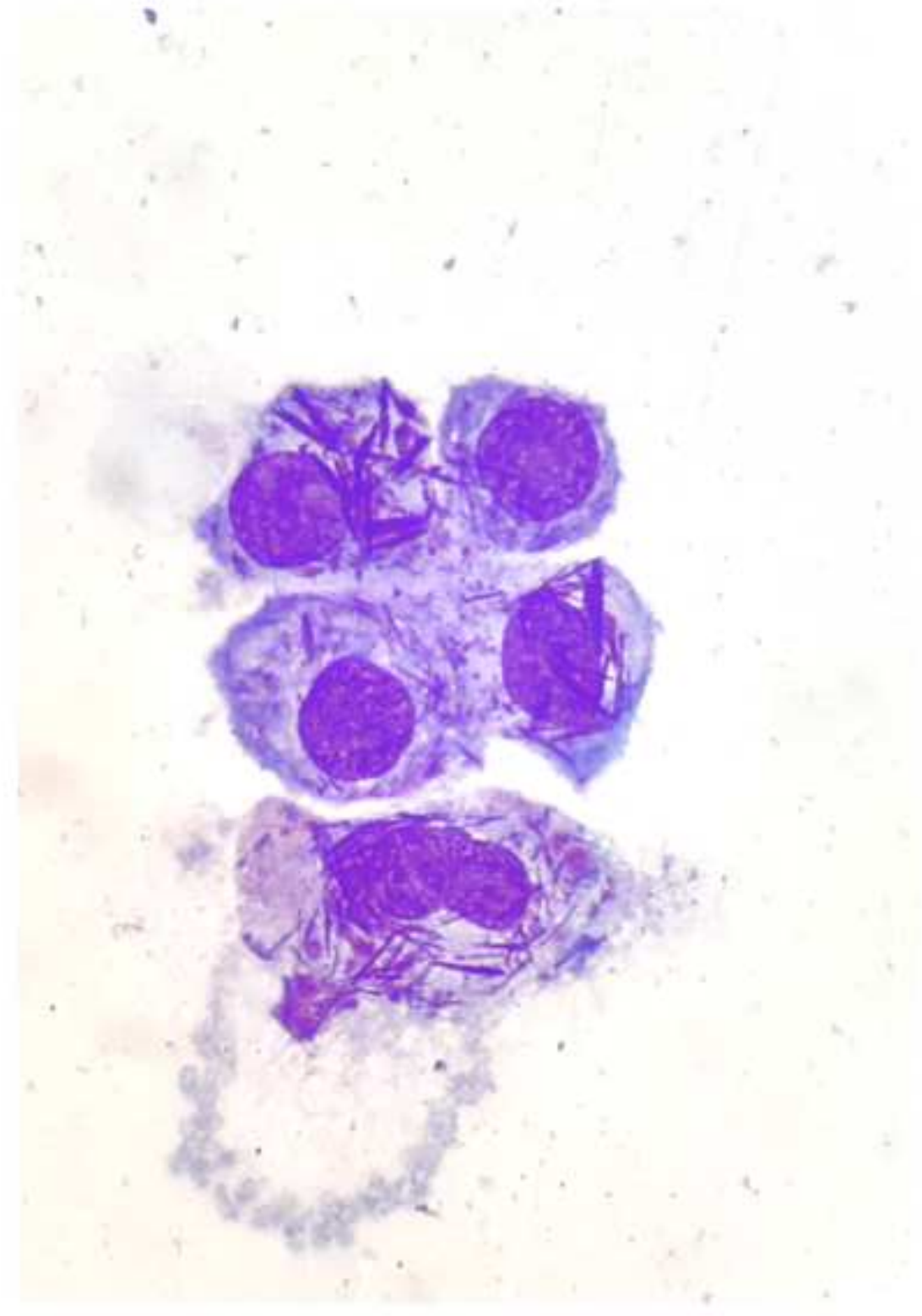
Histopathology (2016), 10.1111/his.12768



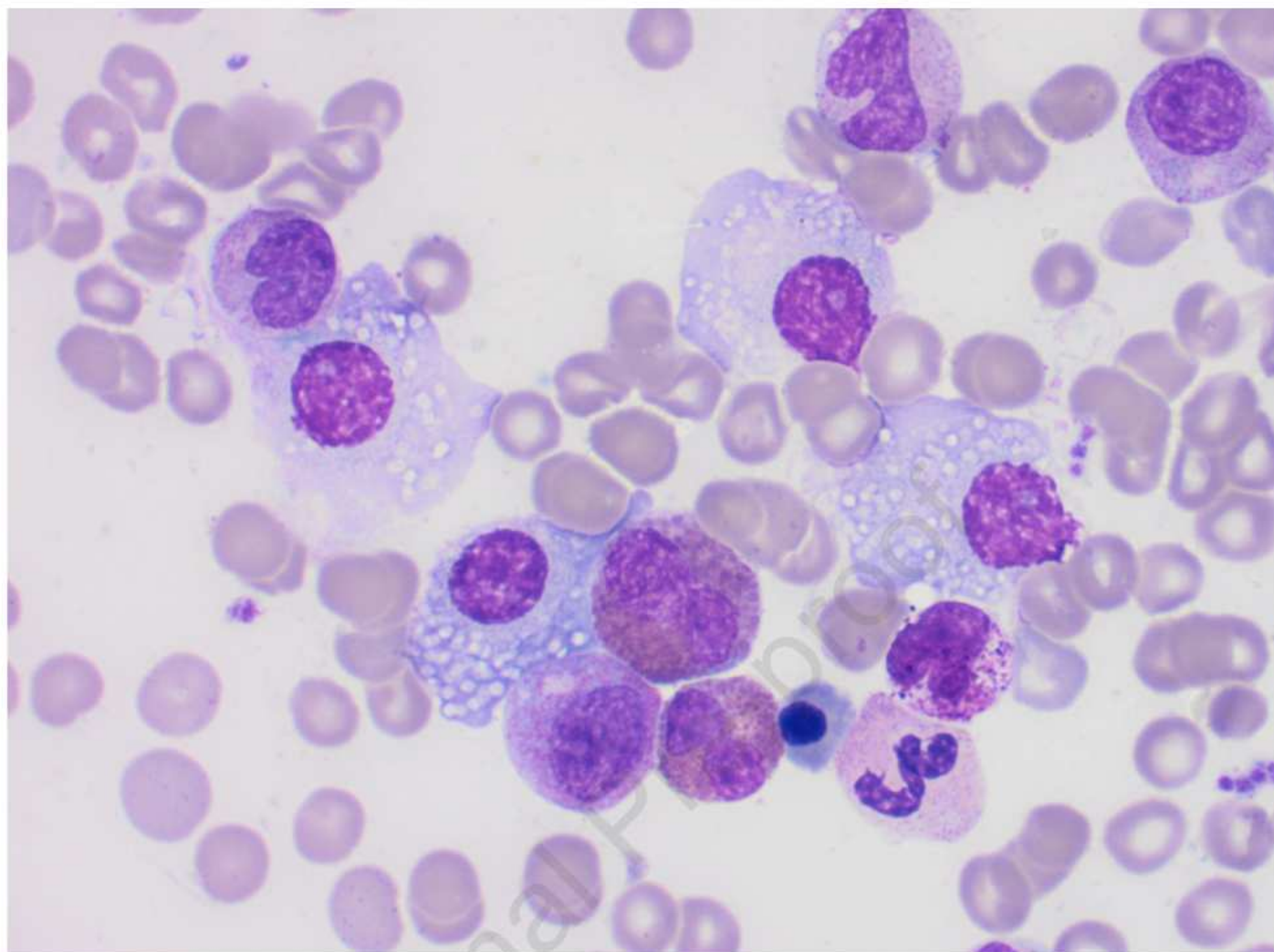


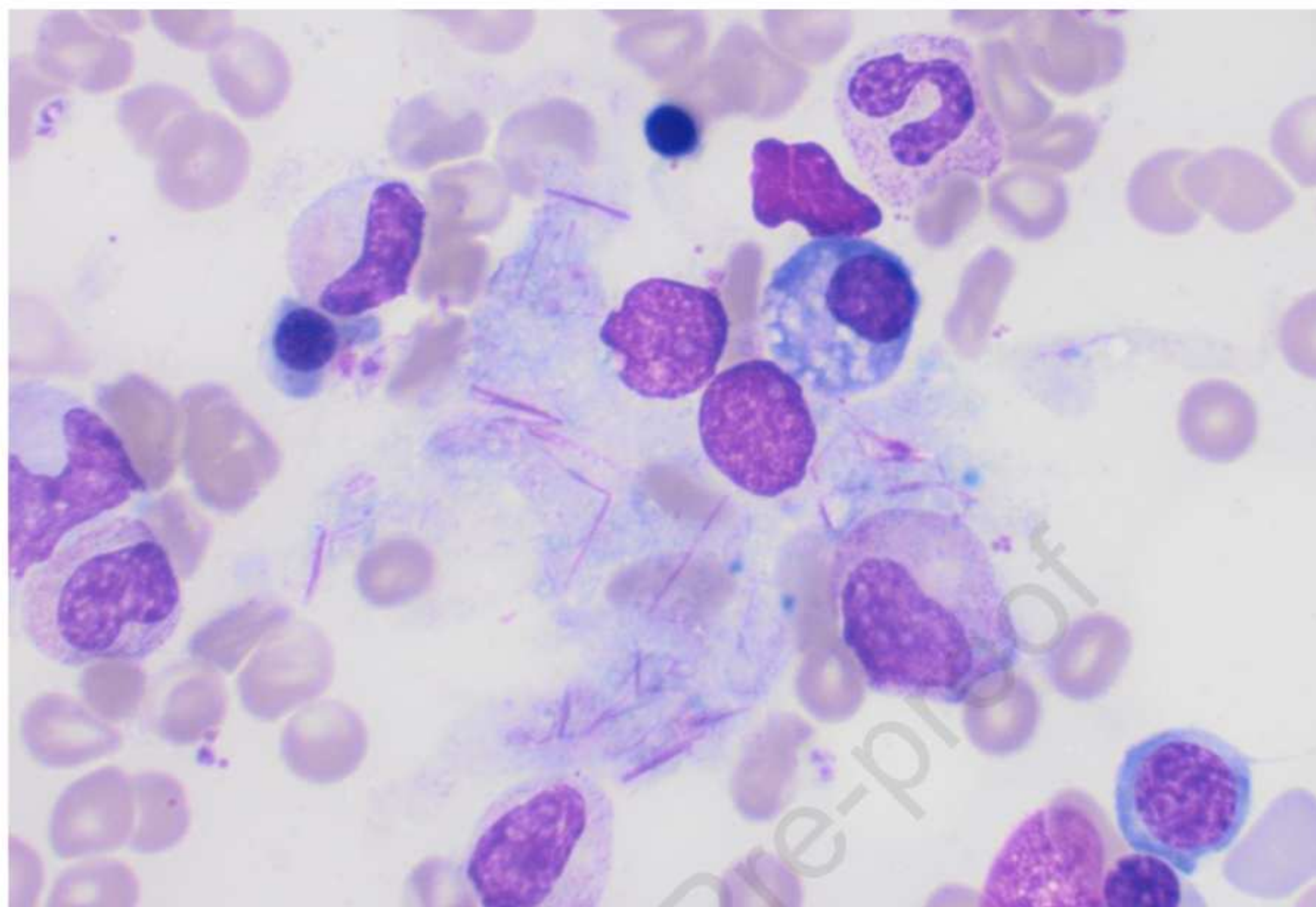


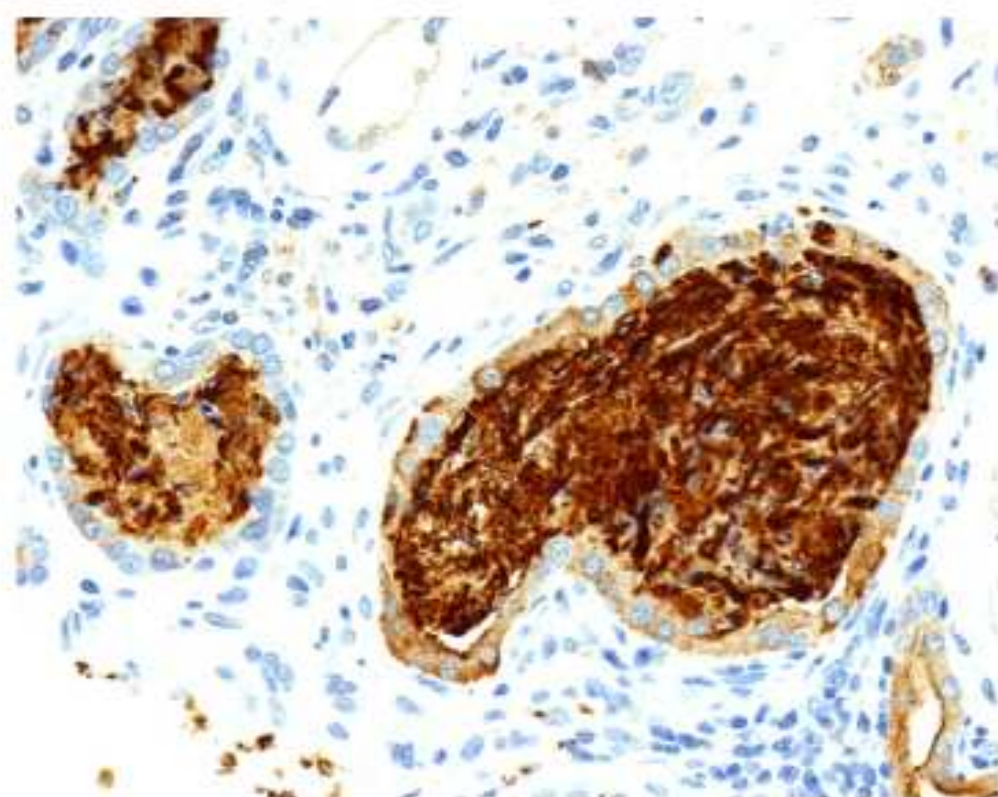
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