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Case Report A SCITECHNOL JOURNAL

Old Disease in a Young Mouse: Case Report for Lymphocytic Leukemia in an 11 Weeks Old Female SCID/Beige Mouse

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Abstract

The SCID (Prkdcscid) Beige (Lystbg) (Fox Chase SCID Beige) strain is an inbred and severely immunodeficient mouse model that is commonly used for tumor biology and xenograft research. The SCID mutation results in defective antibody responses due to improper maturation and function of B cells and T cells. Furthermore, the SCID mutation impairs DNA double-strand break repairing mechanisms. The beige mutation further diminishes the animal's immune system by causing defective Natural Killer (NK) cells. Altogether, these mutations induce susceptibility to diseases such as cancers. Although there are reports of spontaneous hematopoietic cancers developing in immunodeficient mice, this phenomenon is typically seen in advanced age mice. In this report, we discuss a unique case of a spontaneous lymphoma developing in a female SCID/Beige mouse at 11 weeks old. This rare occurrence emphasizes the importance of distinguishing spontaneously arising diseases from xenografted tissues when interpreting studies.

Keywords: DNA; Natural killer; Liver; Spleen; Heart; Lung; Kidney

Case Presentation

Clinical history

An 11 weeks old, sexually intact female SCID Beige mouse was examined, at Tulane University School of Medicine, because of a 2 weeks history of progressive abdominal distension and swelling. The mouse was socially housed with a cohort of 4 other genetically identical mice of the same age and sex. The mice were sourced from Charles River Laboratories, had ad-libitum access to food and water, and had not been experimented on or received treatments of any kind. Cage side examination by a veterinarian noted extreme cachexia; evident by the lack of fat deposit over the pelvic girdle; inappropriate mentation, delayed skin tent, yellow-brown perianal staining, and hunched posture.

Physical examination revealed a grossly distended abdomen with two palpable masses extending the entire length of the anatomical right abdomen. No dental malocclusions were noted on examination. Visual and physical examination of cage mates showed healthy animals with no signs or symptoms of sickness or distress.

Gross necropsy

The mouse was humanely euthanized following the AVMA euthanasia guidelines and approved IACUC protocols. Dissection revealed poor body condition evident by lack of musculature, minimum fat stores, and mild autolysis. Visceral examination showed a severely enlarged liver (Figure 1) and spleen (Figure 2) with rounded edges; ingesta were found throughout the entire gastrointestinal tract. Remaining thoracic and abdominal cavity tissues were grossly unremarkable.

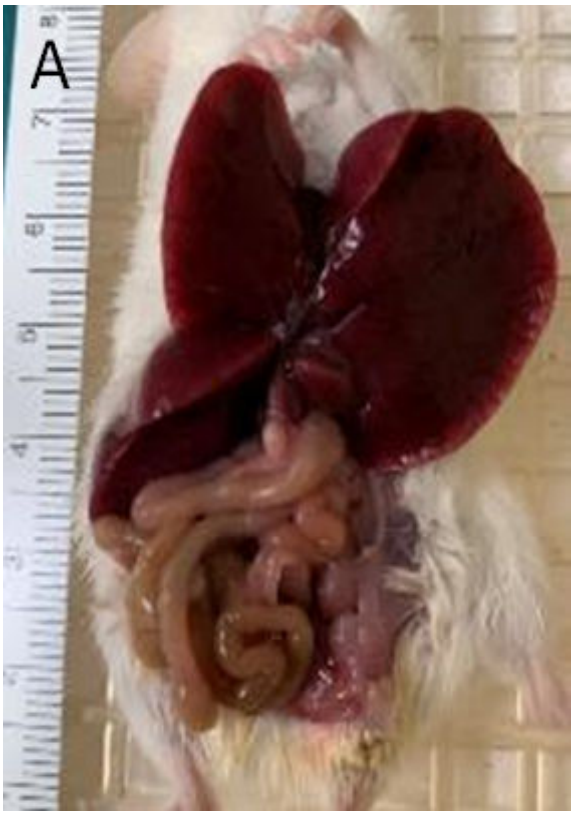

Figure 1: View of reflected liver lobes and exposed GI tract. The liver is enlarged with ruler (cm side) for scale.

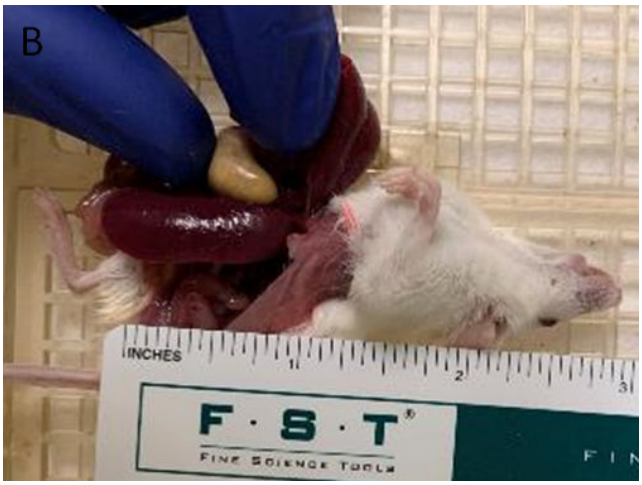

Figure 2: View of exposed spleen with ruler for scale. Enlarged spleen is approximately 2.5 cm in length.

Microscopic Findings

Tissues examined: Liver, lung, kidney, heart, spleen, small intestine, pancreas, and mesenteric lymph node.

Liver: Invading and effacing the normal hepatic parenchyma is a densely cellular, unencapsulated, poorly circumscribed neoplasm. The neoplasm is composed of sheets and aggregates of round cells that surround vessels, expand sinusoids, and compress hepatic cords (Figure 3). Neoplastic cells have round to oval nuclei with finely to coarsely stippled chromatin and 1-2 prominent nucleoli. Neoplastic cells exhibit moderate anisocytosis and anisokaryosis. The mitotic index is >40 mitoses in 10 high powered fields. Neoplastic cells frequently exhibit single cell necrosis. Hepatocytes are frequently atrophic.

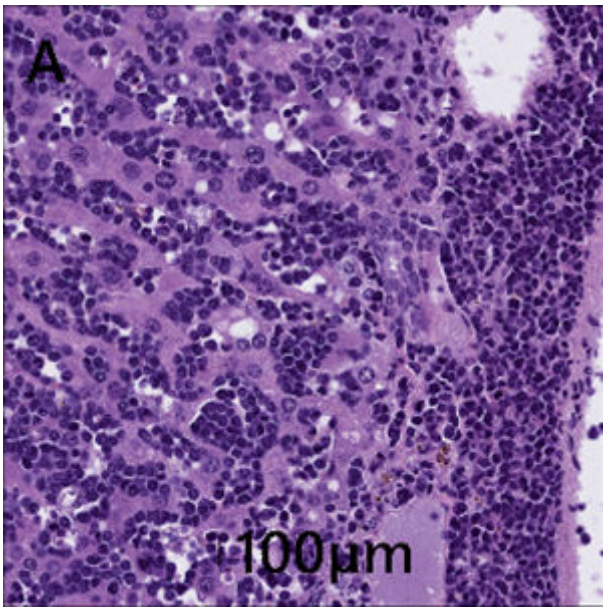

Figure 3: Liver contains neoplastic cells and has a mitotic index of >40 in 10 high powered fields.

Spleen: Diffusely effacing and replacing the spleen is a densely cellular, unencapsulated neoplasm similar to the one described above in the liver. Neoplastic cells form a continuous sheet that replaces the entire splenic parenchyma. Megakaryocytes and rare smooth muscle trabeculae are the only remaining structures to aid in organ identification (Figure 4). Neoplastic cells exhibit moderate to marked anisocytosis and anisokaryosis. The mitotic rate is 5-6 mitoses per 40x field.

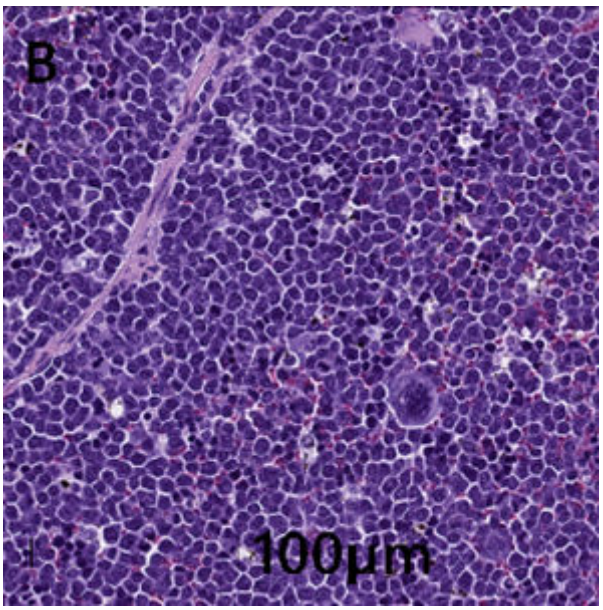

Figure 4: Spleen displays dense cellular neoplasms that diffusely effaces and replaces the normal spleen parenchyma.

Mesenteric lymph node: Invading and effacing the lymph node is a densely cellular, unencapsulated neoplasm similar to the one described in the liver (Figure 5). Neoplastic cells exhibit moderate to marked anisocytosis and anisokaryosis. The mitotic rate is 8-9 mitoses per 40x field. There is a focal area of necrosis along the margin of the lymph node.

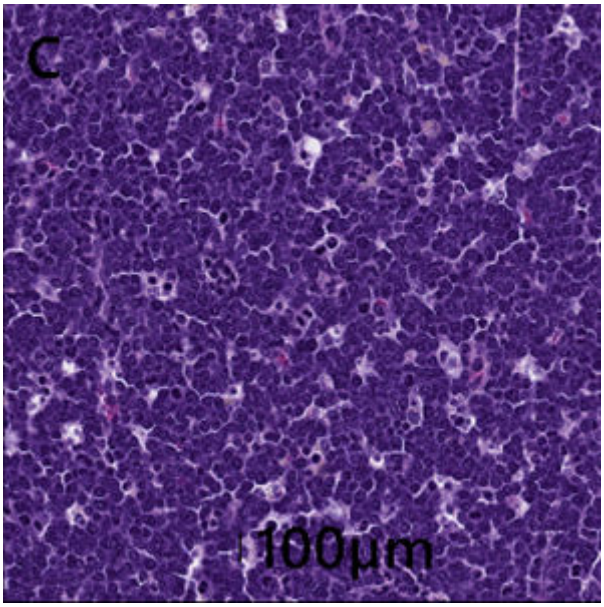

Figure 5: Mesenteric lymph node contains unencapsulated neoplastic cells and has a mitotic rate of 8-9 mitosis per 40x field.

Lung: Alveolar septa and pulmonary vessels are diffusely infiltrated by neoplastic round cells similar to those described above (Figure 6). Invasion into the interstitial and perivascular spaces occurs less frequently. Alveoli multifocally contain hemorrhage and edema.

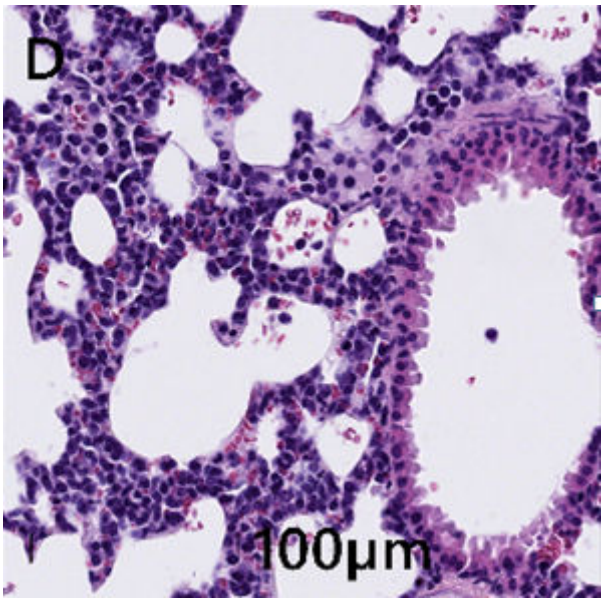

Figure 6: Diffuse infiltration of neoplastic cells into the alveolar septa and pulmonary vessels of the lung can be seen. Furthermore, there is alveoli hemorrhage and edema.

Kidney: Multifocally invading and expanding the renal interstitium surrounding vessels are neoplastic cells similar to those described above in other organs (Figure 7). Neoplastic cells exhibit moderate anisocytosis and anisokaryosis. Mitotic figures are occasionally observed.

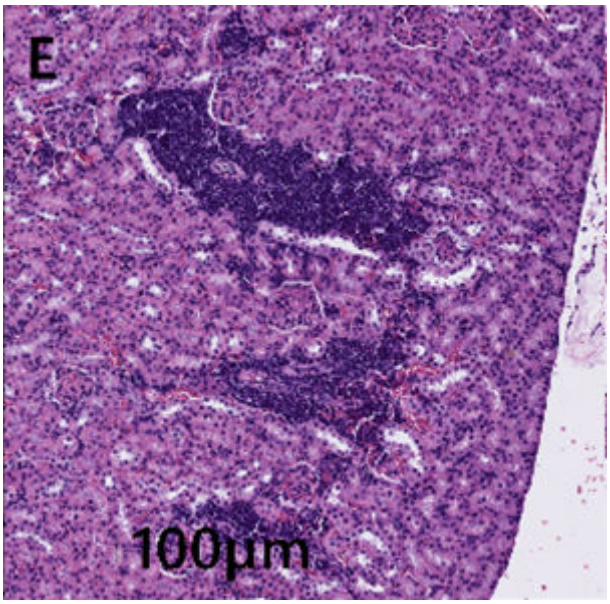

Figure 7: Kidneys display multifocally invading neoplastic cells that have expanded into the renal interstitial spaces. Mitotic figures are occasionally observed.

Heart: The epicardium is multifocally expanded by neoplastic cells similar to those described above (Figure 8). Similar neoplastic cells are seen within vessels and the chambers of the heart.

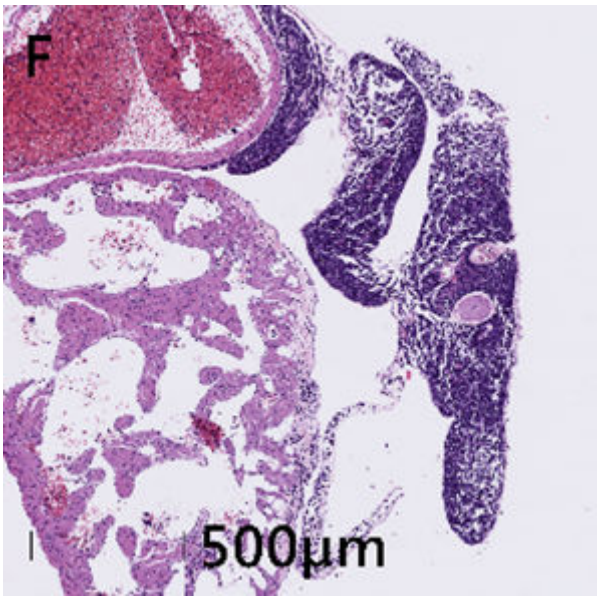

Figure 8: Heart displays multifocal epicardial expansion by neoplastic cells. Neoplastic cells are also detected within the vessels and chambers of the heart.

Small intestine: No significant findings (NSF).

Pancreas: NSF.

Discussion

Immunodeficient mice are popular models for translational research because they are receptive to xenografts of immortalized cell lines, Patient-Derived-Xenograft (PDX) tumors, and primary patient samples. The Fox Chase SCID Beige mouse is an inbred, congenic strain that possess both the Prkdscid (SCID) and Lystbg (Beige) autosomal recessive mutations. The Prkdc mutation, referred to as SCID (severe combined immunodeficiency), eliminates adaptive immunity by preventing V(D)J recombination in developing T and B lymphocytes. Furthermore, this mutation also leads to defects in nonhomologous DNA end joining (NHEJ), a major mechanism for DNA damage repair [1]. The Lystbg mutation is a mutation that causes a severe deficiency of natural killer (NK) cells, reduced bactericidal granulocyte activity, and a reduction in a variety of lysosomal enzymes in neutrophils; the human homologous equivalent of this mutation is Chediak-Higashi syndrome [7,8].

Conclusion

Mouse models with the SCID mutation have been reported to spontaneously develop many different malignancies including rhabdomyosarcomas, myoepitheliomas, and lymphomas. Although the mechanisms for lymphomagenesis in these mice remain unclear, studies suggest that the accumulation of mutations from retroviruses may be a contributor. Lymphoma incidence is positively correlated with mouse age with a study showing 21 weeks as the earliest age of onset. This case report describes the earliest known case of spontaneous lymphoma development in a female SCID Beige mouse

at 11 weeks. Although this is an unusual presentation, we wanted to make researchers aware that it is a possibility and to remind about the importance of vigilance in monitoring research animals.

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