



NOTE

Pathology

Sterile nodular panniculitis with lung and lymph node involvement in a Siberian tiger (*Panthera tigris altica*)

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ABSTRACT. A 2- to 4-year-old uncastrated male *Siberian tiger* (*Panthera tigris altica*) bred in a local wild animal park presented with generalized clinical signs including abdominal pain, fever, lethargy, and anorexia, along with subcutaneous nodules along the trunk. The patient subsequently died of chronic, progressive dyspnea despite 45 days of antibiotic treatment. At necropsy, mesenteric fat inflammation and multiple subcutaneous, peritoneal, and intraabdominal nodules were observed. The lungs demonstrated congestion and heavy coagulation, and necrotic foci were observed on the cut surface. Histopathologically, the nodules were identified as granulomatous fatty tissue with numerous lymphocytes, infiltration with lipid-laden macrophages, and fibrosis. These changes were also noted in the lung. The etiology of this condition remains undetermined.

KEY WORDS: lung involvement, *Siberian tiger*, sterile nodular panniculitis, *Weber-Christian* disease

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Panniculitides are a group of heterogeneous inflammatory diseases involving the subcutaneous fat that are characterized by the development of inflammatory nodules or swelling within subcutaneous tissues. The lower extremities are most frequently affected, and lesions are typically accompanied by systemic symptoms. Despite a wide range of causes, most forms of panniculitis involve the same clinical features.

There are numerous classification schemes for panniculitis in humans. The most useful are those based on the traditional histopathologic distinction between lobular and septal panniculitis, with each form further categorized according to the presence of vasculitis [18]. Lobular panniculitis without vasculitis, previously known as *Weber-Christian* disease in *humans*, is now known as systemic nodular panniculitis. This condition is an uncommon clinical entity and rarely causes or occurs concurrent with death in felines [7]. In cases where death has been attributed to fatal systemic nodular panniculitis, necropsy has revealed widespread involvement of the adipose tissues, including the panniculus; mesenteric, omental, and retroperitoneal adipose tissue; and the intestinal mucosa [15]. Systemic symptoms such as fever, nausea, vomiting, malaise, and arthropathy usually accompany systemic nodular panniculitis and may persist for several weeks or months [22].

A few cases of organ or tissue involvement in nodular systemic panniculitis have been reported in humans, including the liver and spleen [11, 14], heart [22], mesentery [13], bone marrow [3], and lung. With increased awareness of the disease, nodular panniculitis has since been diagnosed in other species, including horses [1, 21], cats [2, 4, 16, 23], and dogs [5, 6, 10, 16, 19], but visceral involvement of this disease has not been reported in any veterinary species to date. In the present report, we describe a case of systemic nodular panniculitis involving the lungs and lymph nodes in a *Siberian tiger* (*Panthera tigris altica*).

A 2- to 4-year-old uncastrated male *Siberian tiger* bred in a local wild animal park presented with generalized clinical signs including abdominal pain, fever, lethargy, and anorexia. The tiger presented with dermal nodules along the trunk and peculiar masses within the abdominal cavity on palpation. The patient subsequently died of chronic, progressive dyspnea despite 45 days of antibiotic treatment. A necropsy was performed within 5 hr of death. Several subcutaneous nodules were present along the abdomen, chest, and back. The dermal nodules were solid, exhibited limited mobility, and varied in size. The largest mass measured 8.5 cm in diameter, while the smallest measured 2.0 cm in diameter. None of the masses showed ulceration or hemorrhage. Similar nodules were also observed within the intraperitoneal fat tissues, including the omental, mesenteric, and perirenal fat. The intraperitoneal nodules were irregular and varied in size from 0.5–10 cm in diameter. The nodules varied in color

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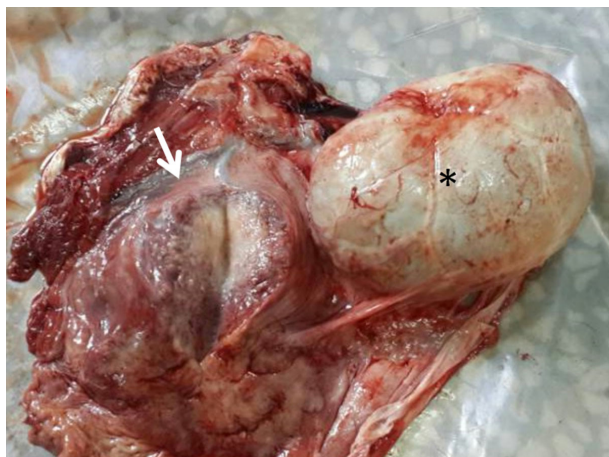


Fig. 1. Perirenal nodule. A large nodule is observed in the perirenal adipose tissue (arrow) of the left kidney (*).



Fig. 2. Mesentery. The mesentery is studded with minute, irregular, white-gray areas.

from red-brown to pale yellow foci resembling fat necrosis, and the cut surface of the nodules was red-gray to pale yellow (Fig. 1). The mesentery was markedly thickened, and the normal lobulation of the fat tissue was absent. Small irregular white-gray spots were studded on the mesentery (Fig. 2).

Both lungs were diffusely enlarged and red-gray, red-black, and white in color. Numerous small white-brown nodules (approximately 0.5 cm in diameter) were observed along the cut surface (Fig. 3). No gross abnormalities were detected in the remaining organs.

Tissue samples were fixed in 10% neutral buffered formalin, processed routinely, embedded in paraffin, sectioned at 3–4 μm , and stained with hematoxylin and eosin (HE) and the special stains (*Fite's Ziehl Neelson stain*, *periodic acid Schiff reaction* and *Gomori methenaminesilver stain*). Frozen sections were stained with *Oil red O* for fatty. The subcutaneous and perirenal nodules showed extensive fibrosis in the adipose tissue, with areas of necrosis. There were areas of inflammation comprising lymphocytes, plasma cells and numerous lipid-laden macrophages. (Fig. 4). At the mesenteric lymph nodes, severe fibrosis and hyalinization were observed in interstitium; the lymph follicles were atrophied and replaced by lipid-laden macrophages (Fig. 5).

Lipid drops, foamy macrophages, decidual alveolar epithelial cells, and infiltrating lymphocytes filled the alveolar space. The lung contained extensive interstitial fibrosis and focal necrosis (Fig. 6). Numerous lipid-laden macrophages and lymphocytes were observed in the lung tissue (Fig. 7A). *Oil red O* staining was performed on the fixed frozen lung sections to detect lipid accumulation within the macrophages. The results revealed infiltration of fat with numerous lipid-laden macrophages throughout the lung parenchyma (Fig. 7B).

After necropsy, *Gram* staining performed on lymph node homogenates was negative. Standard cultures and mycobacterial cultures remained sterile after 15 days and 2 months of incubation of the culture media, respectively.

Based on these collective clinical and histopathologic findings, the patient was diagnosed with nodular panniculitis with lung and lymph node involvement. Sterile nodular panniculitis (*SNP*) is an idiopathic disorder that presents as concurrent inflammation of fat in the abdomen, epidural space, and bone [5, 6]. *SNP* has been reported in *humans*, *cats*, and *dogs*, but this is the first known case of *SNP* in a *Siberian tiger*. In *humans*, the disease is characterized by the development of peculiar inflammatory nodules or swellings in the subcutaneous tissue, frequently in the lower extremities, accompanied by constitutional symptoms. In cases of *dogs* with necrotizing panniculitis, suppurate and granulomatous inflammation associated with the areas of necrosis and pyogranulomatous panniculitis have been observed.

In this case, we were unable to identify any other etiologies besides the panniculitis after the *tiger's* death. After necropsy, we did not obtain biochemical data. Microbial examination was performed, and the bacterial, fungal, and mycobacterial cultures were negative. Reverse transcription-polymerase chain reaction was used to detect canine distemper virus and feline coronavirus RNA in the lymph node samples, and the results were negative.



Fig. 3. Lung. Numerous small, brown-white nodules are observed on the cut surfaces.

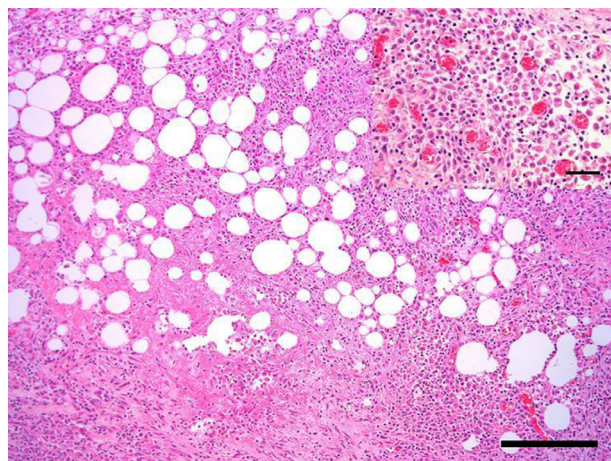


Fig. 4. Subcutaneous nodule. Numerous lipid-laden macrophages and inflammatory cells are infiltrated in adipose tissue. Hematoxylin and eosin (HE) stain. Scale bar=200 μ m. Insert: high magnification of inflammatory cells. Scale bar=50 μ m.

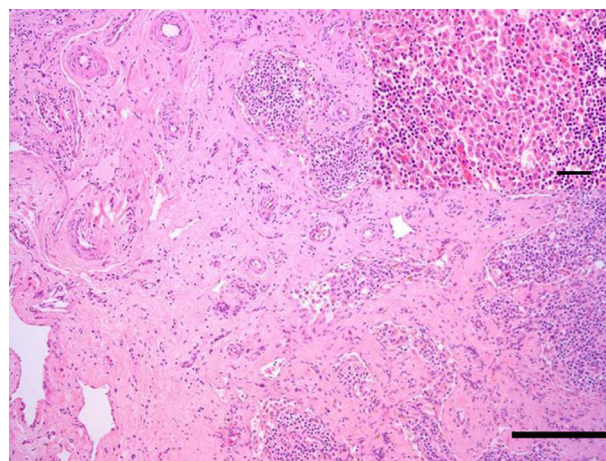


Fig. 5. Severe fibrosis and hyalinization were observed in interstitium. The lymph follicles were atrophied and replaced by lipid-laden macrophages. HE stain. Scale bar=200 μ m. Insert: high magnification of the lymph follicle. Scale bar=50 μ m.

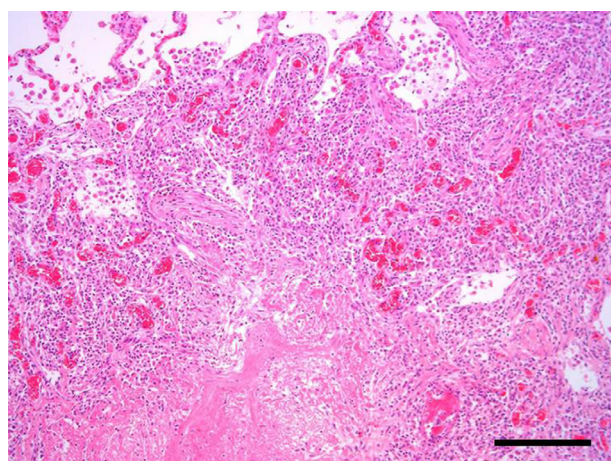


Fig. 6. Lung. Severe interstitial fibrosis is observed. HE stain. Scale bar=200 μ m.

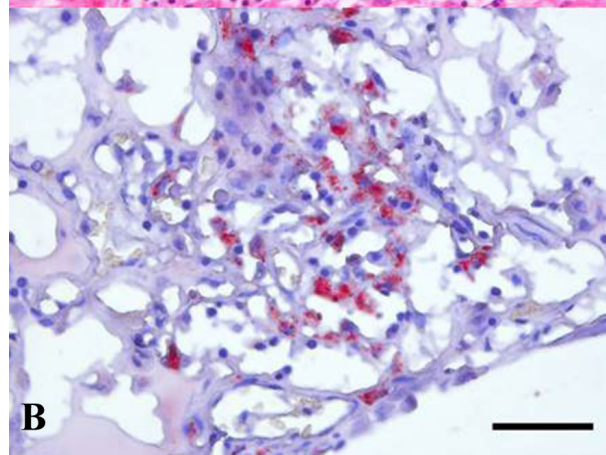
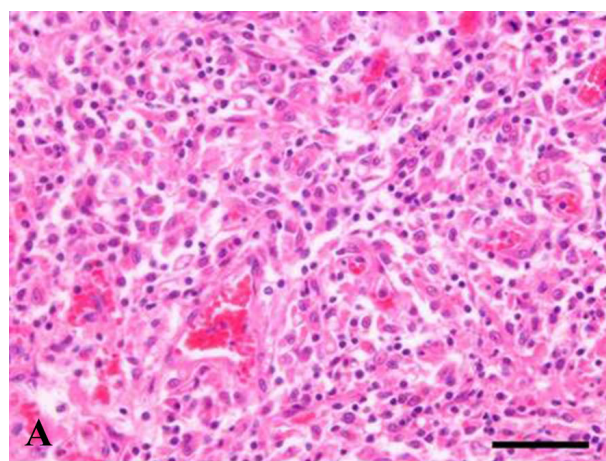


Fig. 7. A. Lung. Numerous lipid-laden macrophages and lymphocytes are observed in the lung tissue. HE stain. B. Numerous oil red O-positive, lipid-laden macrophages are observed scattered throughout the lung. Oil red O stain. Scale bar=50 μ m.

One of the histological features of the present case was variable inflammatory cell infiltration in the subcutaneous adipose tissue, including lymphocytes; plasma cells; and pleomorphic, lipid-laden macrophages. The lung was also infiltrated by the same types of inflammatory cells, and lipid infiltration was observed in the alveolar space. Although the mesenteric lymph nodes were also involved, the lung involvement likely led to the patient's death. Necrotic adipose and connective tissues, including the lung tissue, were followed by fibrosis. Lung involvement may cause a variety of clinical signs, including difficulty breathing, coughing, and the syndrome may not be recognized through respiratory signs.

The pathogenetic mechanism of *SNP* has not yet been fully established. Thus far, the eventual pathological characteristics are similar irrespective of the underlying trigger. The histopathological findings in the present case

are similar to previously reported cases [12]. As an idiopathic disorder, *SNP* may occur as a primary disease or may be associated with any number of other illnesses [7, 16, 17, 19]. A wide variety of causes can induce *SNP*, including trauma, infection, foreign bodies, vitamin E or other nutritional deficiency, drug eruption, insect bite, and neoplasia [16, 17]. It has also been suggested that panniculitis can be classified based on the presence or absence of systemic symptoms. Panniculitis without systemic disease results from trauma or cold; panniculitis with systemic disease is typically due to collagen vascular disease, pancreatic disease, or lymphoproliferative disorders [9]. *Alpha 1*-antitrypsin deficiency is also a major cause of panniculitis in humans [20]. In the present case, no physical or chemical agents were evident in the clinical history. We did not find any evidence of trauma, and infection was excluded based on the laboratory test results. Nutritional (*vitamin E*) deficiency, insect bite, and autoimmune disorder, alone or in combination appear to be the leading causes of *SNP*. Notably, a previous report demonstrated that subcutaneous injection of the rabies vaccine was associated with focal necrotizing granulomatous panniculitis in cats and dogs [8]; however, the present case was not vaccinated, which excludes this particular etiology.

CONFLICT OF INTEREST. The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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REFERENCES

1. Bassage, L. H. 2nd., Parente, E. J., Krotec, K. L. and Meyer, B. S. 1996. Sterile nodular panniculitis associated with lameness in a horse. *J. Am. Vet. Med. Assoc.* **209**: 1242–1244. [Medline]
2. Beccati, M., Peano, A. and Gallo, M. G. 2007. Pyogranulomatous panniculitis caused by *Mycobacterium alvei* in a cat. *J. Small Anim. Pract.* **48**: 664–664. [Medline] [CrossRef]
3. Choi, C. M., Lew, B. L., Lee, S. H. and Sim, W. Y. 2013. Gouty panniculitis also involving the bone marrow. *Acta Derm. Venereol.* **93**: 189–190. [Medline] [CrossRef]
4. Fabbrini, F., Anfray, P., Viacava, P., Gregori, M. and Abramo, F. 2005. Feline cutaneous and visceral necrotizing panniculitis and steatitis associated with a pancreatic tumour. *Vet. Dermatol.* **16**: 413–419. [Medline] [CrossRef]
5. Gear, R. N., Bacon, N. J., Langley-Hobbs, S., Watson, P. J., Woodger, N. and Herrtage, M. E. 2006. Panniculitis, polyarthritis and osteomyelitis associated with pancreatic neoplasia in two dogs. *J. Small Anim. Pract.* **47**: 400–404. [Medline] [CrossRef]
6. German, A. J., Foster, A. P., Holden, D., Hotston Moore, A., Day, M. J. and Hall, E. J. 2003. Sterile nodular panniculitis and pansteatitis in three weimaraners. *J. Small Anim. Pract.* **44**: 449–455. [Medline] [CrossRef]
7. Gross, T. L., Ihrke, P. J., Walder, E. J. and Affolter, V. K. 2005. *Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis*. 2nd ed. Blackwell Science, Ames.
8. Hendrick, M. J. and Dunagan, C. A. 1991. Focal necrotizing granulomatous panniculitis associated with subcutaneous injection of rabies vaccine in cats and dogs: 10 cases (1988–1989). *J. Am. Vet. Med. Assoc.* **198**: 304–305. [Medline]
9. Johnson, M. A., Kannan, D. G., Balachandar, T. G., Jeswanth, S., Rajendran, S. and Surendran, R. 2005. Acute septal panniculitis. A cutaneous marker of a very early stage of pancreatic panniculitis indicating acute pancreatitis. *JOP* **6**: 334–338. [Medline]
10. Mellanby, R. J., Stell, A., Baines, E., Chantrey, J. C. and Herrtage, M. E. 2003. Panniculitis associated with pancreatitis in a cocker spaniel. *J. Small Anim. Pract.* **44**: 24–28. [Medline] [CrossRef]
11. Miller, L. and Kritzler, R. A. 1943. Nodular nonsuppurative panniculitis. *Arch. Derm. Syphilol.* **47**: 82–96. [CrossRef]
12. Mitchinson, M. J. 1965. Systemic idiopathic fibrosis and systemic Weber-Christian disease. *J. Clin. Pathol.* **18**: 645–649. [Medline] [CrossRef]
13. Ogden, W. W. 2nd., Bradburn, D. M. and Rives, J. D. 1960. Panniculitis of the mesentery. *Ann. Surg.* **151**: 659–668. [Medline] [CrossRef]
14. Oram, S. and Cochrane, G. M. 1958. Weber-Christian disease with visceral involvement; an example with hepatic enlargement. *BMJ* **2**: 281–284. [Medline] [CrossRef]
15. Schoen, I., Reingold, I. M. and Meister, L. 1958. Relapsing nodular nonsuppurative panniculitis with lung involvement: clinical and autopsy findings, with notes on pathogenesis. *Ann. Intern. Med.* **49**: 687–698. [Medline] [CrossRef]
16. Scott, D. and Anderson, W. 1988. Panniculitis in dogs and cats: a retrospective analysis of 78 cases. *J. Am. Anim. Hosp. Assoc.* **24**: 551–559.
17. Scott, D., Miller, W. Jr. and Griffin, C. 2001. *Muller & Kirk's Small Animal Dermatology*. 6th ed. WB Saunders, Philadelphia.
18. Torrelo, A. and Hernández, A. 2008. Panniculitis in children. *Dermatol. Clin.* **26**: 491–500, vii. [Medline] [CrossRef]
19. Torres, S. M. 1999. Sterile nodular dermatitis in dogs. *Vet. Clin. North Am. Small Anim. Pract.* **29**: 1311–1323. [Medline] [CrossRef]
20. Valverde, R., Rosales, B., Ortiz-de Frutos, F. J., Rodríguez-Peralto, J. L. and Ortiz-Romero, P. L. 2008. Alpha-1-antitrypsin deficiency panniculitis. *Dermatol. Clin.* **26**: 447–451, vi. [Medline] [CrossRef]
21. Waite, L. H., Cebra, C. K., Tornquist, S. J. and Löhr, C. V. 2006. Panniculitis in a horse with peripancreatitis and pancreatic fibrosis. *J. Vet. Diagn. Invest.* **18**: 405–408. [Medline] [CrossRef]
22. Wilkinson, P. J., Harman, R. R. and Tribe, C. R. 1974. Systemic nodular panniculitis with cardiac involvement. *J. Clin. Pathol.* **27**: 808–812. [Medline] [CrossRef]
23. Youssef, S., Archambault, M., Parker, W. and Yager, J. 2002. Pyogranulomatous panniculitis in a cat associated with infection by the *Mycobacterium fortuitum/peregrinum* group. *Can. Vet. J.* **43**: 285–287. [Medline]