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CASE REPORT

Cytological description of splendore-hoeppli phenomenon in an actinomycetes mycetoma in the skin of a guinea pig

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Abstract

A 10-month-old male guinea pig was presented with an area of alopecia and pruritus on the back. This progressed over 6 months to an ulcerated, painful skin mass. The aim of this report was to illustrate the unique cytological appearance of the Splendore-Hoeppli (SH) reaction, which has rarely been described in veterinary medicine. The mass was sampled using a fine-needle aspiration technique for cytological examination and bacteriological culture. Following cytological diagnosis and bacteriological results, the mass was surgically excised and histopathological examination was performed. Cytological examination of the mass revealed pyogranulomatous inflammation with filamentous bacteria identified by culture to be *Actinomyces* spp. The bacteria were often coated with a moderate amount of red to blue staining material, interpreted to represent the SH reaction. Histopathological examination confirmed the presence of the Splendore-Hoeppli phenomenon (SHP). The appearance of SH in histological specimens is well described in veterinary medicine, but the cytological appearance is not well recognized. This report illustrates well the cytological description of the material which should be recognized as a part of the immune response to insult, and not be mistaken as foreign material.

Keywords Splendore-Hoeppli · *Actinomyces* · Guinea pig · Cytology

Introduction

Splendore-Hoeppli phenomenon (SHP) is a histopathological finding that is described as an intensely eosinophilic, radiating material surrounding infectious agents including bacteria, fungi, and parasites, or biologically inert substances such as suture material (Hussein 2008). It was first described by Splendore in 1908 and Hoeppli in 1932 who studied eosinophilic structures in experimental schistosomiasis in rabbits (Hoeppli 1932; Splendore 1908). Well-defined descriptions histological descriptions of SHP are available. However, it is still not well established how the Splendore-Hoeppli (SH) material is formed, what it consists of, or what function it has in various infections. Some suspect that the formation of SH material functions as a barrier for immune cells, impairing their ability to attack microorganisms and making the infection more severe (Hussein 2008). The SHP has in humans been observed in histological specimens of inflammatory lesions caused by pyogenic bacteria, fungi, or parasites (Gopinath 2018), as well as in fine needle aspirates from subcutaneous breast, lung, and liver inflammatory lesions (Hussein 2008). In veterinary medicine, SHP has been described in histopathology specimens from cutaneous and subcutaneous masses, lung parenchyma, bone, and muscle tissue in cats, mice, rabbits, heifers, and grey seals (Carvalho et al. 2022; Muñoz-Silvestre et al. 2020; Barnett et al. 2019; Murakami et al. 2014). This report includes cytological description of SH reaction, which has not been well described earlier.

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Case presentation

A 10-month-old male guinea pig was presented to the Small Animal Clinic "Din Veterinär" in Helsingborg, Sweden, with a history of pruritus and alopecia on the back. Physical examination revealed no other abnormal findings. A skin scraping was negative for parasites. The animal was treated with selamectin, an antiparasitic spot-on medication. Four months later, the owner noticed a nodule developing on the back in the same area as the original alopecia. The nodule ulcerated 2 months later and the guinea pig was reevaluated. A fine-needle aspirate and material for bacteriological culture was taken from the nodule which then measured 2 × 3 cm. The case was then referred to Fågel & Smådjurskliniken in Lomma, Sweden, for surgical removal of the mass. Upon admittance, the guinea pig was alert but slightly overweight. A wound with a scab formation was noted on the lumbar area overlying a diffuse area of thick and painful subcutaneous tissue. The animal was anesthetized with a combination of midazolam, fentanyl, and medetomidine. Sevoflurane inhaled by mask was used for maintaining anesthesia. The affected area was infiltrated with bupivacaine before incision. An oval incision was made around the mass and the surrounding thickened tissue and down through the muscle layer in order to remove the whole affected area. The subcutaneous tissue was sutured using Vicryl 4–0 and the skin was sutured using Ethilon 4–0. The anesthesia was reversed with atipamezole, flumazenil, and naloxone. Postoperative pain medication included methadone and meloxicam. Postoperatively, the wound became infected, the sutures broke down and the wound healed by the second intention. It had healed completely 1.5 months after surgery and a follow-up 19 months after surgery showed no signs of relapse.

Materials and methods

The fine-needle aspiration biopsy of the mass was performed, and cytological slides were made by spread technique. The slides were air-dried and stained with a Romanowsky-type stain (Giemsa, May-Grünwald, Merck, Darmstadt, Germany) and examined with a light microscope. A bacteriological sample was taken 5 days after the fine needle aspirate by massaging out the material of the wound and was submitted to the Swedish Veterinary Agency (SVA, Uppsala, Sweden) for analysis. For aerobic culture, horse blood agar, bromocresol purple lactose agar, and hematin/yeast agar in CO_2 were used. For anaerobic incubation, fastidious anaerobe agar (FAA) was used. For the identification of bacteria, mass spectrometry–based technology known as matrix-assisted laser desorption ionization time of flight (MALDI-TOF) was performed.

Approximately 6 weeks after the admittance, the mass was removed and fixed with 10% neutral buffered formalin for histopathological examination. The formalin-fixed sample was trimmed, embedded in paraffin, and processed routinely for microscopy. Four-micrometer-thick tissue sections were stained with hematoxylin and eosin for histological examination.

Results

Cytological smears from FNA of the mass revealed highly cellular smears with large numbers of inflammatory cells and extra- and intracellular bacteria amid a bloody background of inflammatory cells comprised of approximately 80% heterophils, 15% macrophages, and 5% lymphocytes and rare eosinophils. Bacteria were present in moderate to abundant amounts and of different forms. Most bacteria were considered to be two morphological types of *Actinomyces* spp. The classical type was a filamentous, branching form. The less recognized, diphtheroid form presented as smaller cocci and coccoid to rod-shaped forms that were very abundant. Another type consisted of a sparse number of cocci, often paired or present in short chains suggestive of *Streptococcus* spp. The filamentous forms were often coated with a moderate amount of elongated, baseball bat–shaped, pale red, or blue-staining extracellular, glassy material that measured approximately 20–40 µm × 3–5 µm, which was interpreted as SH material. Occasionally, it stained negatively or very pale blue (Fig. 1). In some areas, filamentous forms could be seen within the SH material (Figs. 2 and 3). The filamentous bacteria coated with SH material were seen both extra- and intracellularly in macrophages and even heterophils. Macrophages often phagocytized debris and even heterophils.

The cytological conclusion was a pyogranulomatous inflammation with *Actinomyces*-like organism and SH-type reaction.

Histological sections showed multifocal, well-demarcated pyogranulomatous inflammation in the dermis characterized by multiple pyogranulomas. The pyogranulomas had central club-shaped bacterial colonies with basophilic granular material (sulfur granules) surrounded by a ring of sharp, radiating brightly eosinophilic material consistent with a SH reaction (Fig. 4). The bacterial colonies were surrounded by a large number of heterophils. More peripherally, the inflammatory cells were dominated by epithelioid macrophages, a few multinucleated giant cells, and scattered plasma cells and lymphocytes. Furthermore, the pyogranulomas were surrounded by various amounts of fibrous connective tissue with a proliferation of fibroblasts. Figure 5 shows the classical SH reaction around

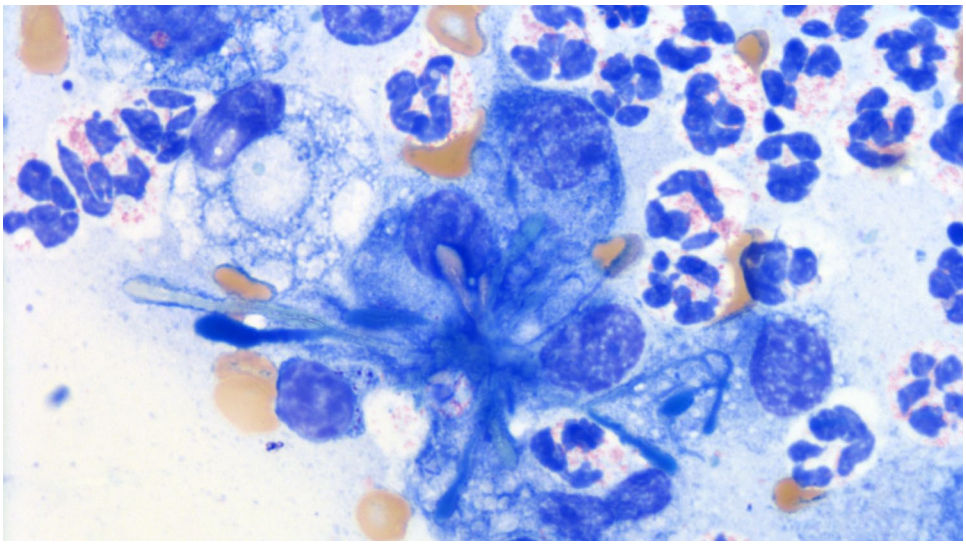

Fig. 1 Cytology of the mass. A cluster of macrophages in the center contained filamentous forms of *Actinomyces* spp. usually coated with blue staining material interpreted to be SH material. The filamentous bacteria appeared to hold about 4–5 macrophages together. Giemsa stain, original magnification was × 1000

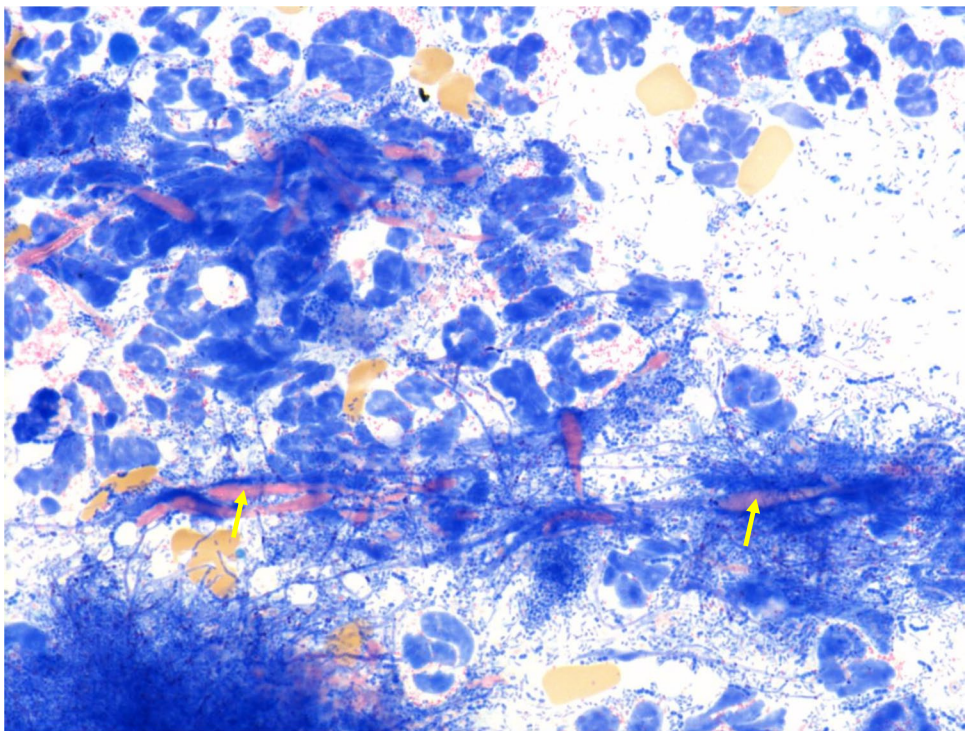

Fig. 2 Cytology of the mass. There are many bacteria of various types, including branching filamentous bacteria (arrow) coated with a red material forming long cylinders interpreted as SH material. Giemsa stain, original magnification × 1000

colonies of *Actinomyces* spp. similar to the cytological pattern.

Bacterial culture revealed sparse growth of three species of bacteria: *Actinomyces* spp. (MALDI-TOF score 2.18), *Streptococcus anginosus* (MALDI-TOF score 2.05), and *Streptococcus constellatus* sp. *pharynges* (MALDI-TOF score 1.89). *Actinomyces* spp. grew in hematin/yeast agar (CO2) after 3 days incubation.

Discussion

SHP is a unique finding in histopathological specimens consisting of deposition of extracellular eosinophilic material that is believed to represent a barrier between causative infectious and noninfectious agents and inflammatory cells. It is described as a radiating, star-like, intensely eosinophilic material around microorganisms or

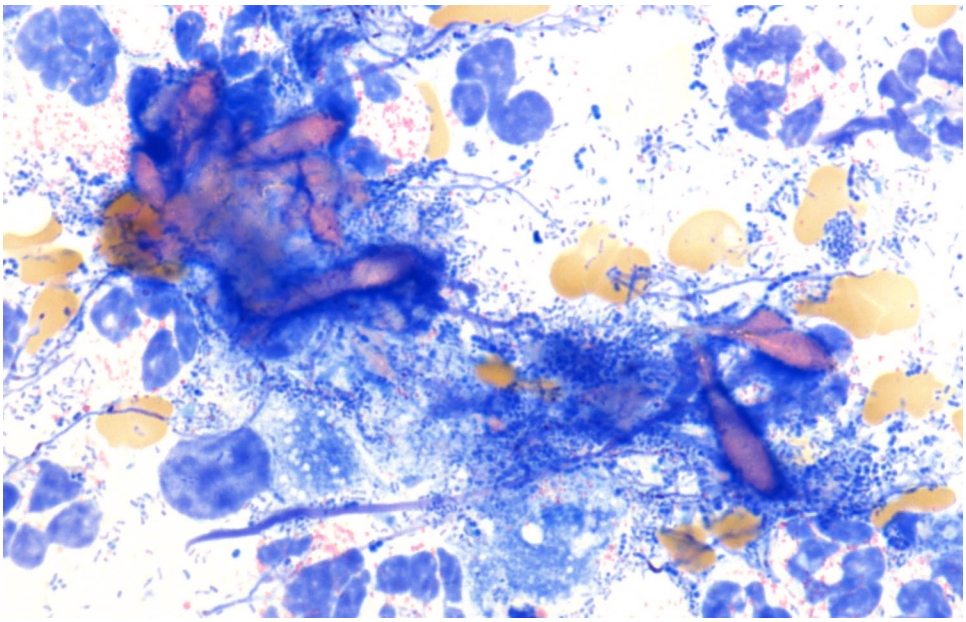

Fig. 3 Cytology of the mass. Numerous bacteria present had different forms. The long, thin branching filaments were considered to be *Actinomyces* spp. The small pleomorphic bacteria were considered to be the diphtheroid form of *Actinomyces* spp. The orange cylindrical structures were considered to be SH material on filamentous forms. Original magnification × 1000

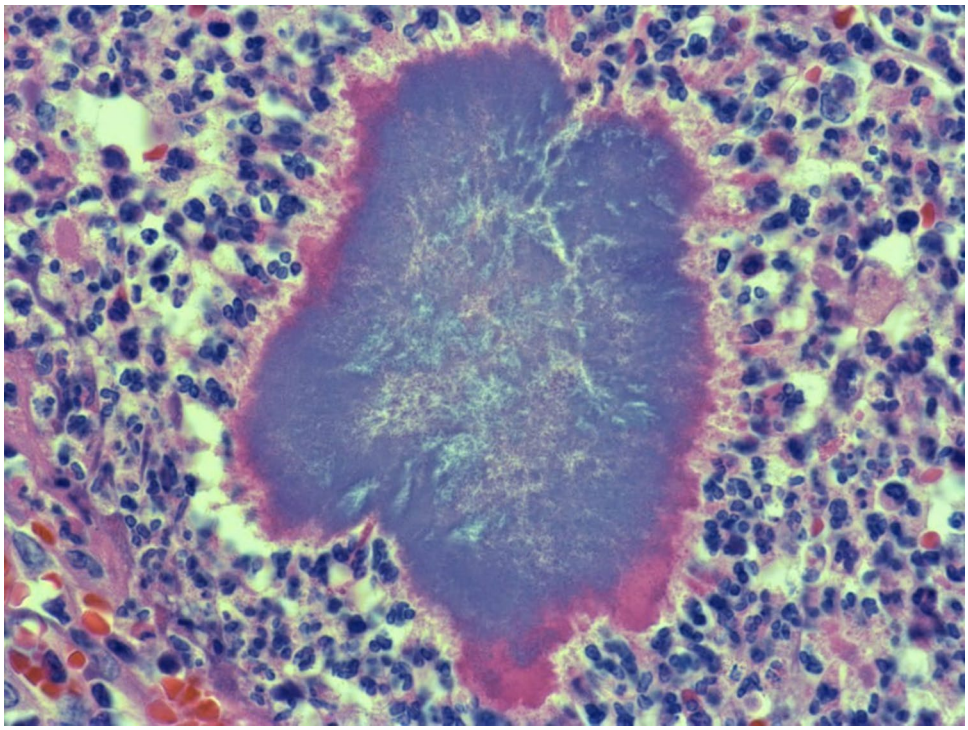

Fig. 4 Histopathology of the mass. A colony of *Actinomyces* spp. bacteria has the red staining typical Splendore-Hoeppli clubbing at the edge. H + E stain, original magnification × 600

biologically inert substances like sutures (Hussein 2008). Its unique appearance allows a reasonably confident diagnosis. In the present case, the SH reaction was morphologically evident on both cytological and histopathological examinations. The SH material stained either basophilic or eosinophilic and was associated with filamentous bacteria which were free and phagocytized within macrophages and heterophils. Bacterial culture demonstrated growth of *Actinomyces* spp., which has previously been documented to induce SHP as discussed later (Masand et al. 2015).

The composition of SH material is not well determined. The eosinophilic material in one case included a protein deposit of precipitated antigen–antibody complexes that stained positive for IgG, IgM, IgA, and complement C3 (Read et al. 2005). In a different case with strong eosinophilic inflammation, the material stained positive for

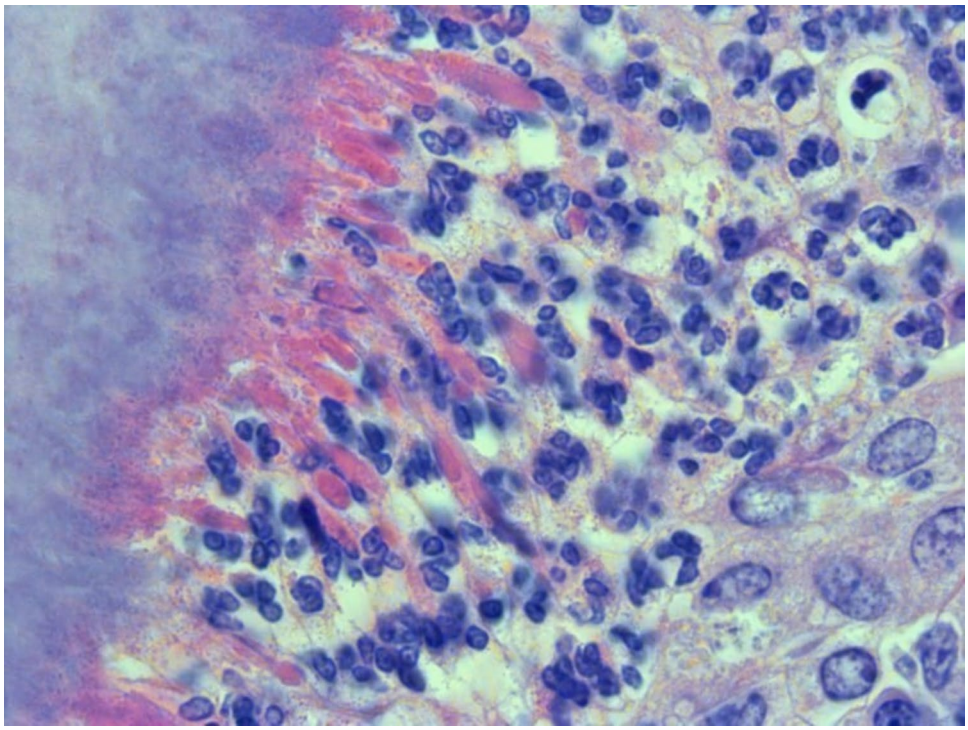

Fig. 5 Histopathology of the typical SH reaction. There is cylindrical clubbing around filaments of bacteria extending out at the edge of a colony. H + E stain, original magnification × 1000

eosinophilic basic protein (EBP), indicating an accumulation of extracellular eosinophilic material that eosinophils normally produce (Acharya and Ackerman 2014). Many eosinophils were noticed in association with the EBP-positive material (Read et al. 2005). EBP is the eosinophilic protein that forms in an acidic environment (Bystrom et al. 2011), which would, if eosinophils were present, explain the red color of the material. In our case report, eosinophils were only rarely observed and therefore the presence of EBP was unlikely.

Cytologically, SH material in samples from humans has been described as elongated rectangular, rhomboid, or rounded dense, glassy, dark crystal-like structures measuring 10–40 × 6–12 µm. The material stained purple to blue on Giemsa stain, blue with Diff-Quik, and orange-pink to greenish when stained with Papanicolau stain (Aragao et al. 2019). In our case, the SH material stained red with May-Grunwald Giemsa stain, unlike that reported in two earlier studies (Aragao et al. 2019; Naik et al. 2014). Antigen–antibody complexes can form in both acidic and basic environments (Talley and Alexov 2010). Colors of Giemsa staining are highly affected by pH; this may explain different staining patterns in our case.

Cytologically, few differential diagnoses for eosinophilic material exist. It could erroneously be interpreted as foreign material, a well-known trigger for pyogranulomatous inflammation (Raskin et al. 2010). Additionally, the material could resemble Charcot-Leyden crystals (CLC) that consist of eosinophil-derived proteins. These share similar shape and staining pattern as SH material, but are more elongated and frequently hexagonal to needle-shaped (Staribratova et al. 2010; Cian and M. P. 2019). To the authors' knowledge, there are no special cytological stains available that could aid in differentiation between these entities; therefore, the evaluation of cytomorphological features remains the strongest tool for differentiating them from each other. Charcot-Leyden crystals can be encountered in any type of inflammatory reaction that causes infiltration of eosinophils and therefore were considered unlikely to be present in our case.

SHP is recognized in veterinary medicine in some diseases and is most often related to pyogenic skin infections caused by various infection agents (Hussein 2008; Padilla-Desgarennes et al. 2012). In cattle, *Actinomyces bovis* is recognized as a causative agent for lumpy jaw disease, which has been documented to cause an SH reaction (Masand et al. 2015). Barnett et al. reported SHP related to infection with parasites in pulmonary vasculature. The SH material was noted in the vascular wall, with nematodes in the lumen of the vessel. Their conclusion was that initiation of SHP was triggered by direct contact of tissue with either the parasite or by chronic exposure to parasitic antigens that occurred during parasite migration through tissue (Barnett et al. 2019). Abscess formation caused by pyogenic *Staphylococcus* spp. has been reported to cause SHP in two cats. In one of the cases, the cat had skin lesions characterized by ulceration, and imprint cytology was interpreted as pyogranulomatous inflammation. Histopathology revealed bacterial colonies surrounded by SH material (Carvalho et al. 2022). In

the other case, SH material was present in histological specimens from subcutaneous, muscle, and bone tissues including bone marrow (França Sde et al. 2014). Studies documenting SHP in both naturally and experimentally infected rabbits and mice are available. These include histological samples of skin pyogranulomas caused by *Streptococcus* spp., *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (Muñoz-Silvestre et al. 2020; Hedley et al. 2019; Bridgeford et al. 2008). In a heifer, SHP was documented in a case of eosinophilic granuloma caused by *Corynebacterium ulcerans*. The bacteria were coated by SH material within eosinophil abscesses that were surrounded by epithelioid cells, lymphocytes, and plasma cells (Murakami et al. 2014). Some authors in these studies speculated that the SH material as well as the inflammatory response could function as a barrier to the host's response to the infection (Murakami et al. 2014; França Sde et al. 2014). This could impede phagocytosis of bacteria, contributing to the chronicity and persistence of infections. The formations of granulomas and sulfur granules are focal lesions walled off from the immune response. Sulfur granules are tightly woven mats of *Actinomyces* spp. filaments which are difficult for immune response to penetrate (Kubo et al. 1980). A study with rabbits associated the drainage of purulent material out to the skin surface led to the resolution of infection (Muñoz-Silvestre et al. 2020; Murakami et al. 2014).

Similarly, in our case, surgical removal of the granuloma containing *Actinomyces* spp. bacteria was associated with the resolution of the infection. *Actinomyces* spp. were often seen in macrophages and even heterophils in the cytological examination. The filaments were often coated with SH material. This suggests that phagocytosis occurred despite the coating of SH material. There was no study performed to identify the rate or magnitude of phagocytosis. Phagocytosis does not indicate if the phagocytes were effective in killing the *Actinomyces* spp.

Actinomycosis is a slowly progressive, chronic infection characterized by pyogranulomatous inflammation (Sykes and Sykes 2014). Culture results are often falsely negative, primarily due to the organism's slow growth, which necessitates days to weeks of incubation and anaerobic conditions. Because other bacteria are much easier to culture than *Actinomyces* spp. and appear earlier during incubation, this may contribute to the commonly found false-negative culture results with *Actinomyces* spp. (Fabre 2023). Moreover, *Actinomyces* spp. are susceptible to being overgrown by other organisms (Sykes and Sykes 2014). As a result, a presumptive diagnosis of actinomycosis can sometimes be reliant solely on cytomorphological findings from aspirated tissue samples (Aragao et al. 2019). In our case, the identification of *Actinomyces* spp. was achieved by the MALDI-TOF mass spectrometry method which analyzes time-of-flight patterns of ionized particles, providing accurate results within a few days. This method allows faster identification of organisms that may be difficult to identify by traditional methods (Ng et al. 2012). *Actinomyces* spp. typically exhibit resistance to phagocytosis, facilitated by the isolation of sulfur granules that inhibit the host's response (Valour et al. 2014). However, in the present case, active phagocytosis of bacteria was cytologically observed by macrophages and, to a lesser extent, by heterophils (Fig. 3).

In addition to *Actinomyces* spp., two species of *Streptococcus* bacteria were isolated from our Guinea pig's lesion. *Streptococcus* spp. bacteria may cause SHP, but coccoid bacteria were uncommonly seen in the cytological samples compared to the numerous filamentous and diphtheroid forms of *Actinomyces* spp. For that reason, *Actinomyces* spp. bacteria were considered to be the most likely cause of the inflammatory lesion.

In conclusion, the SH reaction can be well recognized in cytological samples. This case offers a morphological description of cytological findings in SHP, which is important to recognize when evaluating cytological samples from inflammatory lesions. It should be interpreted as a part of the immune response to insult, and not be mistaken as foreign material.

Author contribution All authors contributed to the study design. Cecilia Trägårdh performed clinical examination, surgical treatment, and biopsy of the mass. Cytological examinations were performed by Luka Ecimovic, Harold Tvedten, and Anna Hillström. Lisa Lindström performed the histological examination. All authors contributed to the final manuscript.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest. The authors have indicated that they have no affiliations or financial interests in the subject matter of this article.

Ethical approval This article does not contain any studies with animals performed by any of the authors.

Informed consent Animal owners gave written consent for the case to be published.

Consent for publication For this type of study, consent for publication is not required.

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