The Answer Is "Snot" What You'd Expect…

Clare C. Brown

Mississippi State University

College of Veterinary Medicine

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Advisors: Nataly Mamaliger, DVM & Amy Lack, DVM, MS, DACVIM

History and Presentation:

Spirit, a 13-year-old American Quarter Horse gelding, presented to Mississippi State University College of Veterinary Medicine's Equine Services on June 25, 2019 for an approximately 1-year history of nasal discharge, ranging from blood-tinged mucus to epistaxis. Spirit's nasal discharge was described as intermittent and unilateral, always from the left nostril. The owners also noted it was associated with a foul odor. Prior to treatment, the discharge occurred about 1-2 times per week and with variable severity. There were no apparent associations with seasonality, diet, housing, exercise, etc. Spirit had lost a significant amount of weight the previous winter, which he since gained back. There were otherwise no other changes noted. Previously a sorting horse, at the time of presentation Spirit was being used for trail riding and was being trained for barrel racing. He was the only animal housed on a 5-acre pasture; however, another horse from the same farm was being treated for strangles at the time. Spirit was up to date on vaccinations, deworming, dental care, and Coggins testing at the time of presentation.

In May of 2019, Spirit's primary care veterinarian prescribed a 2-week course of oral trimethoprim/sulfadiazine (Uniprim), which yielded partial abatement of clinical signs. A week after discontinuation, the epistaxis had resumed in frequency and severity, so a second course of antibiotics was prescribed for 3 weeks, immediately prior to his presentation to MSU-CVM. While on antibiotics, the odor and frequency of the discharge seemed to decrease, and during the course of treatment he only had two episodes of epistaxis. Nasal discharge was last observed 6 days prior to presentation to MSU-CVM.

Upon initial presentation, Spirit was bright, alert, and responsive. He had an ideal body condition score of 5/9. Hydration status was normal, with pink and moist mucous membranes

and a capillary refill time of less than 2 seconds. He had a temperature of 101.0°F, a pulse of 56 beats per minute, and a respiratory rate of 28 breaths per minute. Upon cardiothoracic auscultation, there were no obvious murmurs or arrhythmias, and normal bronchovesicular sounds were present in all lung fields with no crackles or wheezes heard. Normal gastrointestinal motility was auscultated in all four quadrants, and digital pulses were slight to none in all four limbs. Spirit had bloody mucous nasal discharge from his left nostril, with a foul odor. True epistaxis was not observed at the time of examination or throughout his stay in hospital. Mild bilateral ocular discharge was present. All cranial nerve functions that were tested were within normal limits. A bony deformity was evident on the medial aspect of the frontal bone, just to the left of midline.

Diagnostic and Therapeutic Approach:

On June 25, the day of presentation, a complete blood count was performed and revealed a mild anemia with a PCV of 25% (26–42%) and a mild eosinophilia of 1126 /uL (0–1000). Spirit was sedated with intravenous butorphanol and detomidine for rhinoscopy and endoscopic examination of the guttural pouches. The left guttural pouch exhibited slight narrowing of the medial compartment but was otherwise normal, with no fluid present and no gross lesions or any indications of inflammation or infection. The right guttural pouch and larynx appeared grossly normal. On the roof of the nasopharynx, just rostral to the larynx, a raised, irregularly shaped, proliferative lesion was present.

A 4-view series of skull radiographs was also obtained under standing sedation. Stippled soft tissue opaque material was present throughout the left frontal and the left rostral and caudal maxillary sinuses, with top differentials including granuloma formation (such as with fungal etiologies), foreign material, or neoplasia. A sharply marginated fluid line was also present

within the left rostral maxillary sinus, indicative of sinusitis, hemorrhage, or obstruction by the aforementioned soft tissue opaque structure.

On June 26, Spirit was heavily sedated with butorphanol and detomidine for a frontal sinus trephination, with intent to also perform an exploratory endoscopy of the left frontal and caudal maxillary sinuses. Two surgical sites were prepped: one for access to the frontal and caudal maxillary sinus, and one in the event that access to the rostral maxillary sinus was deemed necessary. A circumferential line block with 2% mepivacaine was performed and an incision was made through the skin and periosteum in a half-circle, approximately 1.5 cm larger in radius than the trephine diameter, over the frontal maxillary sinus. The tissue was undermined and reflected from the underlying frontal bone. An opening in the frontal bone was made manually with a trephine and the bone fragment removed. Upon entering the sinus, bloody and necrotic material protruded and flowed from the site. The left frontal sinus was digitally explored through the trephination site. A soft tissue density lesion was palpated, which seemed to occupy the majority of the sinus cavity and extended beyond palpable range. Due to the density of the material, an endoscopy was not feasible and therefore was not performed. Samples of the mass were obtained for biopsy. The site was closed in standard fashion and the head was bandaged with sterile gauze and Elastikon, and recovery was uneventful. Organic iodide powder (1mg/kg PO q24 hours) and trimethoprim sulfa (1mg/kg PO q12 hours) was initiated for empirical treatment of suspected fungal or bacterial disease until biopsy results returned.

Histopathologic examination of the surgical biopsy revealed a neoplasm effacing the normal tissue. Neoplastic cells formed thick mats and papillary structures that extended into the lumen of the sinus. Neoplastic cells appeared to form small acinar structures and sometimes had irregular cilia along apical borders. Mitotic figures were equal or greater to 12 per high powered

field. Large rafts of viable neoplastic cells were also embedded in the mucous and sinus, indicating possibility of spread. Also noted in the biopsy was hemorrhage, mucous, and cellular debris. Given these histologic findings, an adenocarcinoma was the top differential. Several features of the mass were concerning, including the high mitotic rate and presence of clusters of neoplastic cells within the surrounding tissue, indicating a quickly growing and invasive tumor. Due to the poor prognosis, Spirit was euthanized on June 27 and his body was submitted for necropsy.

A post-mortem CT scan of the head was performed. An expansive mass of soft tissue attenuation, admixed with fluid, was present which filled the left aspect of the frontal sinus and extended past midline. Additionally, there was subtle rightward deviation of the nasal septum, and fluid lines were present in multiple sinuses. Cortical thickening of the frontal bone and soft tissue swelling over the frontal bone was also present, consistent with the location of bony deformity observed on physical examination. The site of trephination was also visible.

Notable external findings on gross necropsy examination were consistent with physical examination on presentation. A large, multinodular friable mass occupied and effaced over 95% of the caudal maxillary sinus and extended into the ethmoid. Destruction of the left side of the cribriform plate was noted, and the left olfactory nerve was yellow and rarefied. Sinus and left nasal cavities contained abundant viscous and malodorous fluid, and there was mild rightward deviation of the nasal septum. Within the laryngeal lymph nodes there were multifocal abscesses, which cultured *Streptococcus equi equi,* the causative agent of equine strangles. No other clinically significant gross or histopathologic findings were noted. Histopathology confirmed many of the same features reported in the biopsy, however with further tissues to examine it was noted that neoplastic cells were in fact forming rare rosette and pseudorosettes and not acinar

structures. These findings were most consistent with an esthesioneuroblastoma. Neoplastic cells stained variably positive for the chromogranin immunohistochemical marker, which stains for neuroectodermal tissue. This differentiated the tumor from a carcinoma and lent further support to the final diagnosis of esthesioneuroblastoma.

Pathophysiology:

Spirit was diagnosed with esthesioneuroblastoma. Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is an exceedingly rare sinonasal tumor in equines[1,2]. This tumor is a malignant neoplasm of neuroectodermal tissue, typically arising from the caudal nasal cavity lining the cribriform plate[4,5]. Sinonasal neoplasia is uncommon in horses; in one study, 10.3% of horses presenting for sinonasal disease to a tertiary referral center were diagnosed with sinonasal neoplasia, and of these, only one had confirmed distant metastasis[6]. ENB is a rare tumor even among cases of sinonasal tumors. It is uncommon in humans, accounting for approximately 2–6% of all nasal and paranasal sinus tumors and is even more rarely reported in animals[4,5]. It has been reported in a wide variety of species, with cases being described in dogs, cats, cattle, horses, monkeys, fish, and mice[1-5]. There have been at least 3 published case reports of ENB in domestic horses to date[1,2,3]. Significant similarity is seen in the clinical, morphologic, histologic, and immunohistochemical presentation across species, although wide variation may be seen between individual cases[4].

Clinical presentation of ENB can be variable and nonspecific and is often influenced by the location and extent of tumor development[4]. In horses, common presenting signs include lacrimation, exophthalmos or proptosis of the eye, and epistaxis[1,2,3]. Local tumor growth is frequently unilateral in nature. This tumor can be extremely locally invasive. Distant metastasis is uncommon but has been reported in several species; metastasis has been reported to numerous

organs in humans, and metastasis to liver and lung has been reported in a canine case[7,8]. Only one report of metastasis has been made in a horse, which happened to be to the eye[1].

Because signs are often nonspecific, it is important to formulate a thorough and inclusive differential list. Differentials for epistaxis or nasal discharge in a horse, such as in Spirit's case, should include guttural pouch mycosis, guttural pouch empyema, ethmoid hematoma, coagulation disorders, trauma, bacterial pneumonia of anaerobic etiology, equine induced pulmonary hemorrhage, and, far less commonly, neoplasia. Endoscopy is the first diagnostic of choice for approaching sinonasal disease in the horse[6]. ENB in both humans and domestic species typically have a gross appearance of glistening, polypoid, soft red-to-gray masses with robust vascularization[4]. Advanced imaging such as CT or MRI is the gold standard for determining extent of tumor growth and invasion and may be useful for determining further prognostic information and surgical candidacy[6]. Minimum database, radiography, and cytology may also be useful diagnostics, but histopathology is necessary for definitive diagnosis.

There are no formalized classification systems for ENB in domestic animals[4]. Due to similarities in presentation and biological behavior of ENB between humans and animals, grading and staging schemes are sometimes borrowed from human medicine[4]. Hyam's grading system is largely based on mitotic index and degree of cellular differentiation[4]. The Kadish staging system is based on local spread of the tumor and is the only valuable prognostic indicator for anticipating recurrence and biological behavior of these tumors[4]. Histologically, ENB may be very difficult to distinguish from other sinonasal tumors such as poorly differentiated adenocarcinoma or melanoma[4]. ENB in reported equine cases have been characterized by highly cellular and uniform neoplastic populations with variable mitotic figure counts[1,2]. Rosettes and pseudorosettes are a useful signifying characteristic but are not always present, nor are they

pathognomonic for ENB[1,4]. As with human ENB, reported cases of equine ENB have shown positive immunostaining for chromogranin, neuron specific enolase (NSE), glial filament acidic protein (GFAP), and S-100 protein and are typically negative or weakly staining for vimentin or cytokeratin[1,2,3]; however, there is no characteristic immunochemical profile for these tumors, and staining may vary between individual cases[4].

In humans, surgery, radiotherapy, or a combination of the two are typically the treatment of choice for ENB with no evidence of distant metastasis[4]. Chemotherapy may also be indicated if there is evidence or suspicion of metastasis[4,5]. There is one case report of radiotherapy in a dog that showed success in reducing tumor size, but local recurrence was seen[9]. Several molecular targets are also being studied in humans, but knowledge of success rates is largely limited to case reports[4]. In horses, there is a lack of information on treatment effectiveness and outcome for ENB. Variable success rates for surgical debulking and radiation therapy have been characterized in other sinonasal tumor types in the horse[10]. Success rates are considerably higher for tumors diagnosed early; however, due to the tendency of clinical signs to be very nonspecific and have onset late in the course of disease progression, most presenting cases of equine sinonasal tumors are too advanced to be amenable to successful treatment[10]. Due to the location and extensive degree of local invasion, treatment success rates for ENB would be expected to be comparatively poorer. Prognosis for ENB is generally poor and in humans is based on Kadish staging[4]. Clinical prognostic indicators have otherwise not been established in animals or humans[4]. Because equine species are obligate nasal breathers, this tumor presents an especially poor prognosis in horses, as it can eventually lead to severe respiratory difficulty.

Conclusion:

This case report describes a common presentation of an extremely uncommon neoplasm in a horse and provides an excellent example of the importance of using a problem-oriented diagnostic approach. In cases such as these, formulating and addressing a complete and thorough differential list is paramount. It is also important to keep in mind that primary sinonasal neoplasia in the equine patient is exceedingly rare but should never be completely excluded as an initial differential if the presentation is compatible. Esthesioneuroblastomas are an extremely rare tumor in domestic animals; however, their similarity to human ENB makes them valuable to study for the advancement of both human and veterinary medicine. These tumors classically carry a very poor prognosis and diagnosis and treatment may be complicated. In Spirit's case, the neoplasm exhibited a high mitotic rate and extensive destruction of the sinuses and turbinates with focal invasion into the brain, indicating a grave prognosis that warranted euthanasia.

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