Veterinary Oncology

CASE REPORT

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Suspected olfactory meningioma and synchronous pituitary microadenoma in a canine patient treated with radiation therapy

Isabelle F. Vanhaezebrouck[1*], Carlos R. Mendez Valenzuela[1], R. Timothy Bentley[2], Matthew L. Scarpelli[3], Jeanna Blake[4] and Kari Ekenstedt[4]

Abstract

The authors report on the rare occurrence of dual synchronous primary brain tumors in a canine patient, successful treatment with radiation therapy, and medical therapy with patient stabilization for almost three years. A 12.5-year-old spayed mixed-breed female Labrador was referred to Purdue Veterinary Hospital to treat hyperadrenocorticism of suspected pituitary origin. During MRI imaging, the presence of two possible brain neoplasms was detected: a possible right olfactory bulb meningioma and a microadenoma of the pituitary gland. The patient was treated with a fractionated course of radiation in both tumors, 15 treatments of 3Gy, which limited the tumor growth. Mitotane therapy corrected the hormonal dysregulation. The dog had a normal life for nearly three years and recently passed. Cancer cells were not found at necropsy. No *MEN1* germline mutations were identified in constitutional DNA (from blood) via high-coverage whole genome sequencing.

Keywords Dual brain tumor, Pituitary microadenoma, Meningioma, Radiation therapy, *MEN1*

Background

Multiple distinct malignant tumors are rare in dogs. In a retrospective study, Rebhun and Thamm (2010) [1] reported a ~3% prevalence of multiple distinct primary tumors out of 1,722 dogs presented to the Oncology service at Colorado State University; none of the cases had a primary brain tumor. The description of synchronous primary neoplasms in canine brains (discovery of two anatomically-separated but simultaneous tumors) is even more unusual. In 2007, MacKillop et al. [2] described a basset hound with a coexistent cerebellar tumor and a thalamic neoplasm [2]. Necropsy and pathology exam of this dog identified a medulloblastoma for the cerebellar tumor and an astrocytoma for the thalamic mass. Recently, Pons-Sorolla Casanova, Mariné, Pumarola, and Feliu-Pascual (2023) [3] published a brain collision tumor between a left frontal oligoastrocytoma and a fibrous meningioma (for this case, two tumors of different origins are growing within the same anatomical space at the same time) [3].

*Correspondence:
Isabelle F. Vanhaezebrouck
ifvan@purdue.edu
[1] Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN, USA
[2] Small Animal Teaching Hospital, The University of Liverpool, Liverpool, UK
[3] School of Health Sciences, College of Health and Human Sciences, Purdue University, West Lafayette, IN, USA
[4] Department of Basic Medical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN, USA

Case presentation

A 12.5-year-old 23 kg spayed female Labrador mix dog was referred to the neurology service at Purdue University, College of Veterinary Medicine, for potential hypophysectomy. Three months prior, the dog was diagnosed with hyperadrenocorticism by the referring veterinarian after a wellness visit revealed elevated liver enzymes and the owner reported an increased appetite. The patient's veterinarian performed an ACTH test (138 nmol/l [20-250nmol/l] for basal value and 693nmol/l [200-450nmol/l] post-stimulation). An ultrasound performed by a board-certified radiologist revealed a diffuse increase in liver echogenicity and a bilateral adrenomegaly (0.75cm thickness for the right gland, 1.09 cm for the left gland, normal <0.7cm). The dog was started on S-Adenosyl methionine (SAMe) 425 mg once daily and mitotane 1mg/kg twice daily. The patient's cortisol values stabilized by three months after starting therapy, basal value 141nmol/l [20-250nmol/l] post-stimulation value 298 nmol/l [200-450nmol/l].

Neurology consultation

Upon the first evaluation by Purdue's neurology service, the owner reported intermittent tremors of the pelvic limb (upper part, side non-specified) without any conscious abnormality. The owner also described stumbling or intermittent scuffing of the same leg. The patient had a persistent increased appetite and was regularly panting. Neurological examination was normal except for inconsistent positional ventral strabismus of the right eye. Upon physical examination, a small subcutaneous mass was present on the right flank, and a left caudal rear mass was previously diagnosed as papilloma. Biochemical analysis revealed elevated liver enzymes, hypercholesterolemia, hyperamylasemia, and hyperkalemia (Table 1). Hematology was unremarkable except for clumped platelets. Three survey thoracic radiographs were unremarkable except for the liver size extending beyond the costal arch with rounded margins.

An MRI (GE 1.5T 8 channel-23x, Milwaukee, WI) exam was performed under general anesthesia. A board-certified veterinary radiologist identified a T2W hyperintense, T1W hyperintense mass *(size length 16.2 mm x height 14.2mm, width 8mm)* in the right cerebral hemisphere, within the right olfactory bulb area. The mass was characterized by strong homogeneous contrast enhancement, a broad-based contact with the falx cerebri, and a dural tail. Mild lysis of, or pressure necrosis of the cribriform plate was suspected. The radiologist concluded the diagnosis of a possible meningioma of the right olfactory bulb (Fig. 1). In addition, the neurohypophysis was prominent and displaced to the right and caudally, creating suspicion of a microadenoma based on the displacement (Fig. 1). (*size length 6 mm x height 5mm, width 5mm*). In a study evaluating normal pituitary size on MRI pituitary in dogs, the mean height was 5.1 mm, and the mean width was 6.4mm [4].

Table 1 Biochemical analysis

Test	Result	Flag	Reference Range	Units
Glucose	102		67-132	mg/dL
Blood Urea Nitrogen	16		7-32	mg/d
Creatinine	0.80		0.50-1.50	mg/dL
Phosphorus	4.7		2.2-7.9	mg/dL
Calcium	11.0		9.7-12.3	mg/dL
Sodium	145		138-148	mmol/L
Potassium	5.3	H	3.5-5.0	mmol/L
Chloride	114		105-117	mmol/L
Carbon Dioxide	23		13-24	mmol/L
Anion Gap	13.3		9.0-18.0	mmol/L
Total Protein	6.9		4.8-6.9	g/dL
Albumin	4.0	H	2.3-3.9	g/dL
Globulin	2.9		0.7-3.8	g/dL
ALTv	187	H	3-69	U/L
Alkaline Phosphatase	522	H	20-157	IU/L
GGT	46	H	5-16	IU/L
Total Bilirubin	0.50		0.10-0.80	mg/dL
Cholesterol	309	H	125-301	mg/dL
Amylase	685		378-1033	IU/L
Lipase	1925	H	104-1753	IU/L

First biochemistry analysis. The letter "H" under the flag colum represents a high value. The results, reference range, and unit measurements are provided for each test (*mg* miligrams, *dl* deciliters, *mmol* micromols, *L* Liters, *g* grams, *IU* International units, *U* Units, *ALTv* Alanine aminotransferase, *GGT* Gamma-glutamyl transferase)

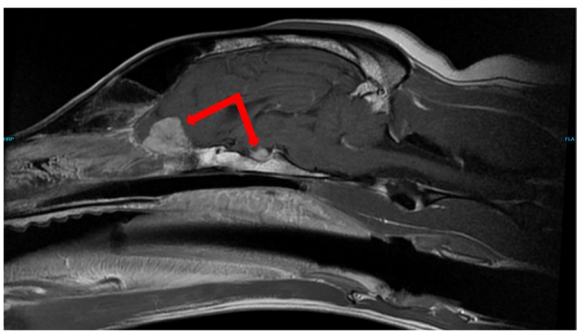

Fig. 1 Sagittal T1 post contrast MRI (GE 1.5T 8 channel-23x, Milwaukee, WI) view: The left red arrow indicates the possible right olfactory bulb meningioma. The right red arrow indicates the likely neurohypophyseal microadenoma (*size length 6 mm, height 5 mm, width 5 mm)* which is prominent and displaced to the right and caudally

Conclusion of the first referral consultation

The patient presented with two simultaneous brain tumors: a suspected right olfactory bulb meningioma without any obvious associated neurologic signs and a hypophyseal microadenoma associated with clinical signs of hyperadrenocorticism. Following a discussion with the owner and the consultation between internal medicine, neurology, and radiation oncology, radiation therapy was the elected treatment for both tumors. Before the radiation enrollment and with the imminent prospect of multiple anesthetic episodes, the dog underwent a cardiac examination with cardiac ultrasound; no cardiac abnormality was reported.

Radiation therapy

Images acquisitions

To complete the treatment plan, the patient was positioned in a vacuum bag with her head immobilized by a bite block and thermoplastic mask (Civco Medical Solutions, Uniframe base plate, Orange City, IA) (Fig. 2). The mask position was indexed to the radiation table couch. Thin slices of 0.625 mm were acquired from our CT scan machine (VCT 64-slices, GE Healthcare, Milwaukee, WI) without and with IV contrast injection (Ultrafast Bayer Healthcare, Wayne, NJ). The acquired images were transferred to our planning computer, Eclipse (Varian Eclipse v11.0, Varian Medical Systems, Palo Alto). The precontrast series images were registered and fused with the MRI (GE 1.5T 8 channel-23x, Milwaukee, WI) T1+contrast series images.

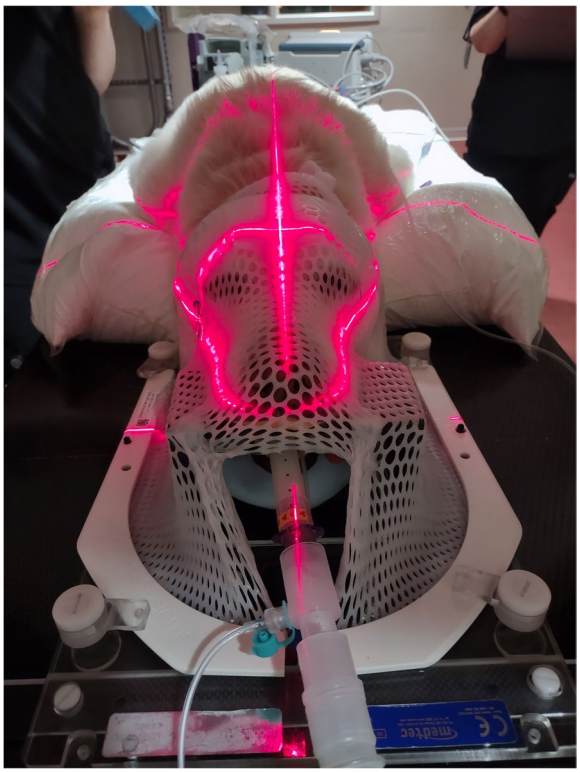

Fig. 2 Patient positioned for treatment plan image acquisition. The patient was positioned and immobilized with various equipment (vacuum bag, thermoplastic mask (Civco Medical Solutions), Uniframe base plate, (Orange City, IA, Uniframe base plate, Orange City, IA)) to aquire the treatment planning images

Radiation Plan Prescription

A definitive treatment with ablative intent (15 fractions of 3 Gy) was prescribed for both suspected tumors. The intracranial meningioma was treated with an intensity-modulated radiation therapy technique (IMRT), and a three-dimensional, four-field treatment was elected for the pituitary microadenoma. Both plans were delivered during the same anesthetic events.

Delivery

The patient was treated every other day with a 6MV linear accelerator (Varian 6EX, MLC Millenium 120 Dose Rate 400MU/mn (Varian Medical Systems, Palo Alto, CA)). The machine is equipped with record verification software (Aria, Varian Medical systems Palo Alto), and patient position accuracy was checked before delivery with port films (Kodak ACR-2000i -Oncocepts Rochester, NY). This patient setup has been previously reported by our institution [5].

For gross tumor volume, the olfactory meningioma (m) and the pituitary microadenoma (p) were considered as separated gross tumor volumes (GTVm and GTVp) and contoured on the T1W+contrast series. For the meningioma, 3 mm margins were added to the GTVm: 2mm for microscopic disease and 1 mm for positioning uncertainty to get the planned tumor volume (PTVm). For the microadenoma, 2mm margins were added to obtain the pituitary planned tumor volume (PTVp). Critical structures were contoured separately (i.e., eyes, lens, optical nerves, optical chiasma, brain, cerebellum, brainstem, spinal cord, and ear bulla).

Two separate radiation plans were designed: 1) an IMRT for the meningioma and 2) a 3D conformal for the pituitary (Fig. 3). Each PTV dose was selected with the intent to receive more than 95% of the dose and less than 107%. A plan summation was realized to verify the cumulative dose and the separation between the two plans [6–8]. Before delivery, the IMRT treatment plan was reviewed by a physicist for quality insurance after comparing the planned fluence and the actual delivery fluence in a diode cylinder Arckcheck ™(Sun Nuclear, Melbourne, Florida). The plan was accepted as the difference in dose registered between the theoretical plan and the real plan delivered on the diodes cylinder matched. In other words, less than a 3% difference was observed

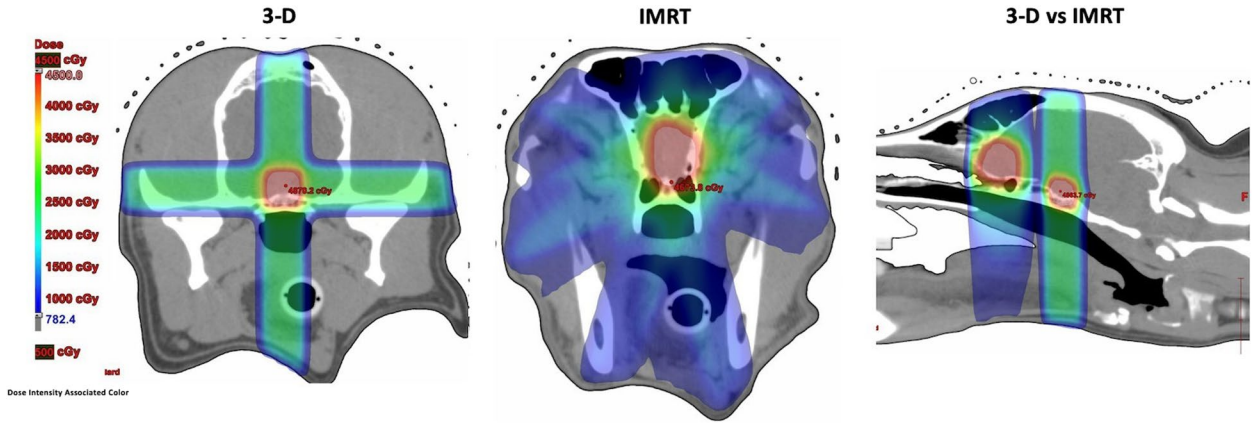

Fig. 3 Dose color distribution from treatment plans. Two axial views, (far left) one corresponding to the pituitary with a 3-D plan, and (middle) the olfactory meningioma with an IMRT plan.The sagital view (far right) visualizes both tumors with their corresponding plans. Scale at left is the color palate matching different doses expresssed in centy gray (cGy) to define the dose intensity associated color for each plan

for over 95% of the diode points selected (3mm distance). The patient received a total of 15 radiation sessions for both sites and recovered uneventfully from these treatments. She was discharged under prednisone 0.5mg/kg once a day to prevent brain radiation secondary effects such as brain edema and inflammation, as well as S-Adenosylmethionine 425mg per day. The mitotane1mg/kg BID was continued.

Patient Follow-up

The patient was rechecked at two weeks and one month after completion of the radiation treatment. The owner did not report any concern for appetite or water intake. Physical exams were unremarkable, and no radiation side effects were observed upon VRTOG (1.0) classification [9]. The steroid prescription was tapered off over six weeks. Six months after finishing radiation, the dog had a complete recheck with the neurology service. The owner reported the dog was doing well and had a stabilized appetite. Mild tremors of the legs were persistent. The neurological exam was unremarkable. The referring veterinarian performed repeat blood work before the recheck with neurology, and hematology results were within normal limits. The cholesterol and amylase values were normal, and the liver enzymes improved in comparison to the first visit but were still mildly elevated GGT 20u/l (RI 0-11u/l); ALKP 343 u/l (RI 23-212 u/l), ALT 125u/l RI(10-125U/l). Following the neurology consultation, the patient had an MRI under general anesthesia. The radiologist concluded that the size of the pituitary microadenoma remained stable, and the size of the intracranial meningioma was reduced (*size: length 10.5 mm x height 12 mm, width 6 mm*. The owner declined further rechecks, but regular phone calls ensured the patient's health for over two years. Three years after the initial neurology consultation, the patient was brought to the emergency service for general fatigue, locomotion incapacity, and progressive decline in quality of life. The owner elected compassionate euthanasia and allowed necropsy.

Necropsy

On gross exam, a frontal mass was present in the right cerebral hemisphere measuring (*size: length 17mm x height 12 mm, width 10 mm). T*he pituitary mass *(length 7 mm x height 6. mm, width 5mm)* was also observed grossly. Multiple adhesions were present at the level of the frontal mass. On histopathology, moderate adrenal cortical nodular hyperplasia and multifocal hemosiderosis were visualized. The liver had mild chronic centro- lobular and periportal fibrosis. The frontal mass consisted only of fibrosis and multifocal microgliosis; no neoplastic cell population was observed. Similarly, no significant histologic findings were seen in the pituitary gland.

Genetic analysis

Germline mutations in the *menin 1 (MEN1)* gene are known to lead to "multiple endocrine neoplasia type 1" (MEN1) syndrome in people [10–14], which is characterized by the development of multifocal neoplastic endocrine lesions together with other non-endocrine tumors, such as central nervous system meningiomas [10, 15–17]. Genetic analysis was carried out to explore this patient's *MEN1* gene for germline (constitutional) mutations.

After obtaining informed, written consent for participation from the owner, an EDTA whole blood sample was obtained from the patient for genetic analysis (Purdue University IACUC #1901001840). DNA was extracted via a standard phenol-chloroform extraction

method and then subjected to whole-genome sequencing (WGS) using Illumina HiSeq 150bp paired-end reads, with an average of 21X coverage. Raw data quality control and variant calling were performed utilizing a previously described standardized bioinformatics pipeline [18]. The sequence reads were trimmed using Trimmomatic [19] and aligned to the canine reference genome assembly CanFam4 [20] using the Burrows-Wheeler Aligner [21]. Variant calling was performed using GATK's HaplotypeCaller [22], identifying single nucleotide polymorphisms (SNPs) and indels. BCFTools 1.17 [23] was used to identify private variants in the patient dog compared to WGS from seven hundred thirty -control dog genomes from genetically diverse breeds, assuming no other dog in the WGS population carried the same disease allele. Private variants were analyzed assuming both an autosomal recessive and autosomal dominant mode of inheritance, and functional effects of variants were predicted with Ensembl Variant Effect Predictor [24]. Variants predicted to have a high or medium impact on the resulting amino acid sequence were prioritized for further investigation. Each medium or high-impact variant-containing gene was filtered through VarElect [25], which prioritized genes based on how often the provided phenotypic terms "meningioma" and "pituitary tumor" appeared in conjunction with that specific gene in other gene-centric databases. Two hundred sixty-five heterozygous variants of high or moderate effect were identified under the assumption of dominant inheritance, but no apparent candidate genes previously associated with MEN1 were identified. Only three variants of high or moderate impact were identified under an assumption of recessive inheritance, and again, no evident candidate genes previously associated with MEN1 were identified. Finally, the integrative genomics viewer software [26] was used for manual visual inspection of the entire candidate gene *MEN1*; this failed to identify any more significant, structural private variants in the affected dog.

Discussion and conclusions

Meningioma is described as the most prevalent tumor in canids [27–29]. The standard of treatment consists of surgery, radiation therapy, or both, depending on tumor location, surgical expertise, and access to a radiation facility. Prognosis with symptomatic medical management only (anticonvulsive drugs, steroids) is limited; mean survival of 75 days [27]. Dogs receiving radiation therapy have a median life expectancy of 1.5 to 2.5 years [27–31]. The radiation therapy options are a fractionated course or using stereotactic techniques [32–38]. Recently, veterinary radiation oncologists have opted for stereotactic radiation techniques, which require less anesthesia and patient hospitalization, with treatment realized in less than a week (usually three fractions, although a unique fraction is possible). Two recent publications [30, 31] reported survival expectancy with stereotactic techniques as similar to or less favorable than fractionated protocols [27–29]. Pituitary tumors are often treated with radiation therapy, as the number of veterinary hospitals with surgeons trained for hypophysectomy is still limited. Prognosis is size dependent [32, 33, 39].

A diagnosis of macroadenoma is less favorable than a diagnosis of microadenoma, and even if radiation therapy controls the tumor growth, the hormonal stabilization of secreting tumors is inconsistent [31, 39]. A hormonal control rate of around 40 % has been reported [31, 32, 39]. In recent years, pituitary tumors have also been treated with less radiation fractions (hypofractionation) and stereotactic techniques. The results have been disappointing regarding survival: six to ten months for the median [30, 31] versus one to two years with fractionated treatments [34, 39]. The presently described patient had a good quality of life, and the hyperadrenocorticism was stabilized with adequate cortisol values for over three years; this is above the median survival reported in the literature for both diseases. A limitation of our study is the absence of pathology results before the radiation treatment for the suspected meningioma. This would have been useful for diagnostic confirmation and the genetic investigations that could have been performed on DNA or RNA from the tumor sample. At necropsy, no tumor cells were observed, only fibrosis, suggesting either the radiation had cured the neoplasia or some remaining tumor cells were still present but at very low quantities, requiring more histological sections.

In people, reports of intracranial meningioma with coexisting pituitary tumors are rare. Case reports mention 1) the occurrence of meningioma in the sella turcica after the treatment of a pituitary tumor either by surgery or radiation, with eventual recurrence of the pituitary tumor, and 2) the occurrence of pituitary tumor after the treatment of meningioma in the same area [38, 40]. A larger cohort retrospective study described seven pituitary adenomas and distant intracranial meningiomas. 20% were associated with growth hormone production, and 30% were classified as prolactinomas [41].

The frequency of meningiomas in patients with MEN1 syndrome is being reported more frequently [42, 43]. Patients with MEN1 syndrome usually have several endocrine tumor disorders, such as tumors of the adrenal glands, pituitary, parathyroids, endocrine pancreas, and carcinoids, often together with non-endocrine tumors of smooth muscles, skin, and the central nervous system, among others. This case study describes a patient with only one endocrine neoplasia, a pituitary tumor. Furthermore, the whole genome sequencing of constitutional

(blood) DNA failed to identify any *MEN1* variants. It should be noted that the WGS methodology used (150bp paired-end reads) is not ideal for discovering large structural rearrangements, so it is still possible for a *MEN1* variant to have been missed. As mentioned above, without pre-treatment tumor samples, we could not sequence tumor DNA or RNA; it was also impossible to carry out any proteomic evaluations for MEN1 or other proteins in its pathway.

In conclusion, this case study described a rare dual synchronous brain tumor presentation. A 12.5-year-old spayed female Labrador mix was treated with radiation therapy for a suspected olfactory meningioma and an ACTH-secreting pituitary microadenoma. The dog responded well to simultaneous treatment of both tumors for almost three years. Whole genome sequencing of constitutional DNA did not reveal any possible *MEN1* mutations. At necropsy, residual tumor could not be identified.

Abbreviations

Gy	Gray
DNA	Deoxyribonucleic Acid
ACTH	Adrenocorticotropic Hormone
SAMe	S-Adenosyl Methionine
MRI	Magnetic Resonance Imaging
IMRT	Intensity-Modulated Radiation Therapy
GTV	Gross Tumor Volume
GTVp	Gross Tumor Volume of the pituitary
GTVm	Gross Tumor Volume of meningioma
VRTOG	Veterinary Radiation Therapy Oncology Group
GGT	Gamma-Glutamyl Transferase
ALKP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
MEN1	Multiple Endocrine Neoplasia Type 1
WGS	Whole Genome Sequencing
SNP	Single Nucleotide Polymorphism

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Authors have approved the submitted version (and any substantially modified version that involves the author's contribution to the study);
Authors have agreed both to be personally accountable for the author's contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Authors' contributions

Conception, IV. Design of the work IV, TB, KE. Data Acquisition, TB, IV, CMV, JB. Analysis, IV, CMV, JB Interpretation of data IV, MS, KE, MS. Drafted work and substantively revised it, IV, CMV, TB, MS, KE.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical review and approval were waived for this case report as it exclusively involved the analysis of clinical data from a patient treated with standard-of-care procedures. Genetic research analysis WGS was approved by Purdue University IACUC committee(IACUC #1901001840) with owner consent.

Consent for publication

Owner has agreed to use patient data for a research publication.

Competing interests

The authors declare no competing interests.

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