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Instruction To Authors

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ACKNOWLEDGMENTS

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Primary melanoma of the central nervous system

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Primary melanoma of the central nervous system (CNS) is extremely rare, accounting for fewer than 1% of all melanomas. Primary CNS melanoma, as opposed to metastatic melanoma, is usually caused by melanocytes in the leptomeninges. These melanocytes arise embryologically from neural crest cells, underlining the distinct developmental of CNS melanomas [1,2]. Clinically, for intracranial located lesions nonspecific symptoms such as headache, focal neurological deficits, or seizures may occur, whereas for spinal lesions presenting symptoms may be back or neck pain along with a gradual, asymmetrical myelopathy. Magnetic resonance imaging and cerebrospinal fluid (CSF) cytology, are essential in finding these lesions, but conclusive diagnosis relies on histological confirmation [3].

Molecular and genetic profiling has shed light on the pathophysiology of primary CNS melanoma, identifying common alterations in genes such as BRAF, NRAS, and c-KIT, comparable to cutaneous melanomas [1-3]. However, primary CNS melanomas have specific biological characteristics. Although they develop slower than metastatic lesions, their location and surgical inaccessibility lead to poor prognosis [3]. The disease's rarity has made it difficult to establish uniform treatment methods. Surgical resection remains the cornerstone of management, sometimes augmented by adjuvant therapies such as radiation or targeted immunotherapy, depending on the mutational profile [3]. Recent advancements in checkpoint inhibitors and BRAF/MEK inhibitors have showed promise in extending survival in advanced cases, while their efficacy in primary CNS melanoma especially warrants further research [3].

Despite improvements, there are still significant gaps in our understanding and treatment of primary CNS melanoma. Because of the rarity of cases, thorough clinical studies are not possible, hence therapy is guided by case reports and brief series [2-3]. Multidisciplinary approaches that include neurosurgery, oncology, and radiation therapy are critical to improving patients' outcomes. Future research should focus on molecular characterization and tailored therapy development, which could open up new pathways for precision medicine (1-3). Increased awareness, as well as improved diagnostic techniques, are required to improve early detection and prognosis for this rare but complex disease.

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REVIEW

Natural Compounds for Glioblastoma Treatment

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ABSTRACT
The most frequent malignant tumor of the central nervous system in adults with a dismal prognosis is glioblastoma (GBM). Although surgery, radiation, and chemotherapy are currently available therapeutic options, the median survival span for GBM is still short, usually 15 months, with only a small percentage of patients surviving for up to 5 years. Flavonoids, curcuminoids, alkaloids, and other natural substances have reported to have anti-tumor properties and can inhibit angiogenesis, promote apoptosis and affect several signaling pathways. Herewith, we review the current evidence on natural compounds for glioblastoma treatment.

Keywords: Natural compounds, glioblastoma, alkaloids, flavonoids

ΠΕΡΙΛΗΨΗ
Ο πιο συχνός κακοήθης όγκος του κεντρικού νευρικού συστήματος σε ενήλικες με κακή πρόγνωση είναι το γλοιοβλάστωμα. Παρόλο που η χειρουργική επέμβαση, η ακτινοβολία και η χημειοθεραπεία είναι σήμερα διαθέσιμες θεραπευτικές επιλογές, η διάμεση επιβίωση είναι μικρή, περίπου στους 15 μήνες, με μόνο ένα μικρό ποσοστό ασθενών να επιβιώνει έως και 5 χρόνια. Τα φλαβονοειδή, τα κουρκουμινοειδή, τα αλκαλοειδή και άλλες φυσικές ουσίες έχουν αναφερθεί ότι έχουν αντικαρκινικές ιδιότητες και μπορούν να αναστείλουν την αγγειογένεση, να προάγουν την απόπτωση και να επηρεάσουν διάφορες σηματοδοτικές οδούς. Στην παρούσα ανασκόπηση παρουσιάζουμε τα τρέχοντα στοιχεία σχετικά με τις φυσικές ενώσεις για τη θεραπεία του γλοιοβλαστώματος..

Λέξεις κλειδιά: φυσικές ενώσεις, γλοιοβλάστωμα, αλκαλοειδή, φλαβονοειδή.

INTRODUCTION

Glioblastoma (GBM), is the most common malignant tumor of the central nervous system (CNS) with poor prognosis. Currently, the therapeutic interventions include surgery, radiotherapy and chemotherapy, however, the median survival period of GBM still remains short, ranging from 14 to 16 months with only few patients may reach up to 5 years (1).

Several drugs are FDA approved for GBM, with temozolomide (TMZ) being the most standard chemotherapy. Nevertheless, TMZ extends the median survival by only 2.5 months, while higher TMZ doses can cause systemic toxicity (2). In addition, most drugs fail to penetrate the blood-brain barrier (BBB), which allows the selective permeation of certain low molecular weight substances and blocks several chemotherapeutic agents (3). Due to the failure of classical chemotherapies and targeted drugs, research efforts have focused on the use of less toxic substances. Various natural substances are therefore evaluated for their potential as therapeutic agents for GBM patients (4). These natural products may restrict tumor growth or induce GBM cell death. Herewith we discuss some natural compounds that may be used to treat GBM (Table 1).

Table 1. Natural compounds that have been used to treat GBM and their function.

NO	NATURAL COMPOUNDS	FUNCTION
1	Alkaloids • Moschamine • N-(p-coumaroyl) serotonin	Cell viability reduction Cell death induction Cell cycle arrest
2	Curcuminoids • Curcumin	Apoptosis– Autophagy induction Cell cycle arrest Changes in gene expression and in molecular signaling
3	Flavonoids • Quercetin	Apoptosis induction Cell cycle arrest Cell proliferation and viability reduction Cell migration and angiogenesis inhibition
4	Coumarins • Osthole • Umbelliferone, • Esculin • 4-hydroxycoumarin • 5-methoxypsoralen	Apoptosis – Autophagy induction Cell cycle arrest Signaling pathway inhibition
5	Other • Carotenoids • Terpenes • Tannins	Cell proliferation and viability reduction Cell migration inhibition Apoptosis induction Cell cycle arrest

NATURAL COMPOUNDS

Alkaloids

Alkaloids are a class of basic, naturally occurring organic compounds, that contain at least one nitrogen atom. They are derived from amino acids and can be synthesized by plants and some animals as secondary metabolites. Alkaloids exhibit significant effects, such as anti-neoplastic, anti-inflammatory, analgesics, local anesthetic and pain relief, antimicrobial, antifungal and many other activities (5). Regarding GBM several alkaloids have evaluated for possible anti-glioma effect.

The indole alkaloid N-(p-coumaroyl) serotonin (CS) has anticancer and antioxidant properties. In the U251MG and T98G glioblastoma cell lines, CS treatment results in decreased cell viability, cell death, and cell cycle arrest at G2/M and S-phase. Additionally, there was a dose-dependent rise in CD15 and CD71 expression and no change in CD24/CD44/CD56 expression. There was also a dose-dependent increase in caspase-8 activity. Zebrafish were used to text toxicity and even at a concentration of 1mM no mortality was found (6).

Moschamine is an indole alkaloid that has cycloxygenase inhibitory and serotoninergic effects. Using flow cytometry, the effect of this agent on the cell cycle, apoptosis (annexin-propidium iodide), and the expression of CD24/CD44/CD56/CD15 was tested in two glioblastoma cell lines. Treatment with moschamine significantly reduced cell proliferation in glioma cell lines tested, while induction of cell death and cell cycle arrest was confirmed. In addition, there was a dose-dependent decrease in CD24 and CD44 expression. Moschamine, also showed no toxicity in zebrafish even at a concentration of 1mM (7).

Curcuminoids

Curcuminoids are natural polyphenol compounds derived from turmeric. Turmeric (Curcuma longa) is a member of the ginger family. Curcumin is one of the main components and it has long been used as food and in traditional medicine in South Asia. Many preclinical studies have demonstrated the anticancer effects of curcumin and other curcuminoids in various types of tumors, including glioblastoma (8). Curcumin induced protective effects in normal cells and multiple cytotoxic effects in tumor cells, such as apoptosis, autophagy, modulation of oxidative stress, cell cycle arrest, changes in gene expression and in molecular signaling (9,10). Targeting the PI3K/Akt signaling pathway, a crucial regulator of cancer cell survival, proliferation, and resistance to apoptosis in glioblastoma, has been demonstrated to be possible with curcumin. Other signaling pathways that may be modulated by curcumin are the NF-κB, P53, Janus kinase/signal transducer and activator of transcription, MAPK and Sonic Hedgehog [11]. Recent studies also demonstrated that curcumin has a radiosensitizing effects in glioblastoma. One study pretreated cells with curcumin using U87 and T98 glioblastoma cell lines before subjecting them to 2 Gy or 4 Gy radiation treatments. Trypan blue exclusion and MTT assays were used to measure cell viability and proliferation, respectively, in order to compare the effects of the combined treatment to those of curcumin or radiation alone. CompuSyn software was used to investigate synergistic effects, and flow cytometry was used to evaluate cell cycle progression. When compared to each treatment alone, the results demonstrated that the combination of radiation and curcumin dramatically decreased cell viability in both cell lines. Furthermore, compared to ei-

ther treatment alone, the combination treatment caused a more noticeable G2/M cell cycle arrest. Curcumin and temozolomide, interestingly, also promoted the mortality of tumor cells [12].

Flavonoids

Flavonoids are polyphenolic compounds which are composed by plants as secondary metabolites. Their primary functions are to draw pollinating insects and protect plants from UV.

The ability of flavonoids to penetrate the blood-brain barrier is a significant characteristic with regard to glioblastoma. This process is achieved through transcellular diffusion, carrier-mediated transcellular transport or paracellular diffusion through tight junctions between the endothelial cells of the BBB (13). In both types of diffusion, the smaller flavonoids are in favor because of their molecular size.

Quercetin is a natural flavonoid that showed anticancer activity. Regarding glioblastoma, this agent exhibited significant effect. Quercetin dramatically reduced glioma cell migration and invasion and reduced the viability of glioblastoma cells both in vitro and in vivo. Additionally, quercetin decreased the expression levels of EMT-related markers and reversed the EMT-like mesenchymal phenotype. Additionally, quercetin inhibited glioblastoma's GSK-3β/β-catenin/ZEB1 signaling [14]. In U373MG cells, quercetin treatment resulted in cell death and decreased cell viability. Furthermore, quercetin therapy at high doses decreased the cell viability of four glioma stem cell lines, but had no discernible effect on the other two. In glioma stem cell lines, quercetin treatment increased the p16-INK4 mRNA and protein levels [15].

Coumarins

Coumarins are a class of compounds derived from plants. They are produced as secondary metabolites, and when iron availability is limited, their primary function is to facilitate iron absorption. They are lactones, structurally constructed by a benzene ring fused to a-pyrone ring. Coumarins have been extensively studied as medicinal candidates for drugs to treat various types of diseases. Strong pharmacological activity, low toxicity and high bioavailability are properties that make coumarin to occupy an important place in medicinal chemistry. Several efforts have been made in developing coumarin-based antioxidant, antimicrobial, anti-inflammatory, anti-neurodegenerative and anticancer agents (16). Recently, 4-methylumbelliferone, a natural coumarin derivative without associated adverse effects , increased the effect of temozolomide on metabolic activity and proliferation in both U251 and LN229 glioblastoma cell lines. Furthermore, this agent increased the effect of temozolide in cell migration and MMP-2 activity [17]. Among other coumarins, Osthole has been proven to be the most effective in glioma cell lines. Cell death is produced through apoptosis and, to a lesser degree, via autophagy [18].

Other natural compounds

Carotenoids, terpenes and tannins are, also, natural compounds which have been studied as a possible treatment in glioblastoma. Astaxanthin and Fucoxanthin showed an ability to suppress cell proliferation and migration in glioblastoma cell lines (19-21). Natural terpenes display anticancer properties by inducing apoptosis and cell cycle arrest (22). Concerning the tannins, tannic acid induced antiglioma activity, including cell viability inhibition, apoptosis induction and cell cycle arrest (23).

CONCLUSION

Natural compounds are constantly gaining ground in the treatment of various chronic diseases such as GBM. Research efforts have been focusing on them due to their special features consisting of low toxicity and high bioavailability. By reducing cell viability, suppressing cell growth, inducing cell death, and causing cell cycle arrest, these substances have already shown significant anticancer effect against GBM in vitro. However, additional research and validation in orthotopic glioma models are needed.

CONFLICT OF INTEREST

Authors declare no conflict of interest, financial or otherwise

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Not applicable

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TITLE

Epidemiology of Intracranial Tumors in Ioannina, Greece (2003-2023)

Eleni Romeo, MD, MSc[1], Athanasios Gkampenis MD[1], Pantelis Bagiorgas MD[1], Georgios Kafritsas MD[1], Anna Goussia[2], George A. Alexiou, MD[1], PhD, Spyridon Voulgaris, MD, PhD[1]

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ABBREVIATIONS LIST
GBM: Glioblastoma, CUP: Cancer of Unknown Primary, N/A: not applicable,
SEER: Surveillance, Epidemiology, and End Results, WHO: World Health Organization

ABSTRACT

Objective: We conducted a retrospective study to determine the epidemiology of intracranial tumors in our country based on the data of cases that underwent surgery in our clinic.

Material and Methods: We collected and reviewed all cases of intracranial tumors that were surgically treated at the Neurosurgery Department of the University Hospital of Ioannina from 2003 to 2023.

Results: From the beginning of 2003 to the end of 2023, 823 cases were included in our study, involving adult patients aged 19-89 years, with a mean age of 56.6 years. The most common tumor was meningioma, accounting for 32% of cases, followed by glioblastomas, metastases, and gliomas other than glioblastoma. Gliomas, including glioblastomas, made up 37% of the tumors that were surgically treated, making them the most frequent type of both primary and overall brain tumors. Among the secondary brain tumors, the most common primary site was the lung, accounting for 43.55% of cases, followed by tumors of unknown primary origin. Between the two decades, we observed an overall decrease in the number of cases surgically treated in our clinic. However, the total number of gliomas increased, mainly due to a rise in glioblastoma cases.

Conclusions: The current study represents the first epidemiological research on brain tumors in the adult population of our country. Gliomas are the most common type of tumor, primarily due to the high number of glioblastomas, the incidence of which appears to have increased in the last decade. Finally, according to our study's data, there is a trend of decreasing overall brain tumor numbers.

Keywords: intracranial, tumor, epidemiology, glioma, meningioma.

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Πραγματοποιήσαμε μια αναδρομική μελέτη για τον καθορισμό της επιδημιολογίας των ενδοκράνιων όγκων στην χώρα μας σύμφωνα με τα δεδομένα των περιστατικών που αντιμετωπίστηκαν στην κλινική μας.

Υλικό και Μέθοδος: Συλλέξαμε και αξιολογήσαμε όλα τα περιστατικά με ενδοκράνιο όγκο που υποβλήθηκαν σε χειρουργική εξαίρεση στη Νευροχειρουργική Κλινική του Πανεπιστημιακού Νοσοκομείο Ιωαννίνων από το 2003-2023.

Αποτελέσματα: Από την έναρξη του 2003 ως το τέλος του 2023, 823 περιστατικά συμπεριλήφθηκαν στην μελέτη μας και αφορούσαν ενήλικες από 19-89 ετών, με μέση ηλικία τα 56.6 έτη. Ο συχνότερος όγκος ήταν το μηνιγγίωμα σε ποσοστό 32%, ακολουθούμενα από το γλοιοβλάστωμα, τις μεταστάσεις και τα λοιπά γλοιώματα. Τα γλοιώματα μαζί με την προσθήκη των γλοιοβλαστωμάτων αντιστοιχούσαν στο 37% των όγκων που αντιμετωπίστηκαν και αποτέλεσαν τον πιο συχνό τύπο όγκου τόσο σε πρωτοπαθείς όσο και σε συνολικούς όγκους. Από τους δευτεροπαθείς όγκους του εγκεφάλου η πιο συχνή πρωτοπαθή εστία ήταν ό πνεύμονας σε ποσοστό 43,5%, ακολουθούμενη από τους όγκους αγνώστου πρωτοπαθούς εστίας. Μεταξύ των δυο δεκαετιών παρατηρήσαμε μια συνολική μείωση του αριθμού των περιστατικών που χειρουργήθηκαν στην κλινική μας. Ωστόσο ο συνολικός αριθμός των γλοιωμάτων αυξήθηκε κυρίως λόγω της αύξησης των γλοιοβλαστωμάτων.

Συμπεράσματα: Η παρούσα μελέτη αποτελεί μια επιδημιολογική έρευνα για τους ενδοκράνιους όγκους στον ενήλικο πληθυσμό της χώρας μας. Τα γλοιωμάτων αποτελούν τον πιο συχνό τύπο όγκου και αυτό οφείλεται κυρίως στον μεγάλο αριθμό γλοιοβλαστωμάτων, η συχνότητα των οποίων φαίνεται να παρουσιάζει μια αύξηση την τελευταία δεκαετία. Τέλος, σύμφωνα με τα δεδομένα της μελέτης μας, υπάρχει μια τάση μείωσης του συνολικού αριθμού των ενδοκράνιων όγκων.

Λέξεις κλειδιά: ενδοκράνιος, νεόπλασμα, επιδημιολογία, γλοίωμα, μηνιγγίωμα

INTRODUCTION

Brain Metastases are the most common brain tumors in adults. Up to three out of ten patients with systemic malignancy will be diagnosed with brain metastases at any age [1]. The most common primary tumors that will lead to brain metastases are lung cancer, breast cancer and melanoma, followed by kidney and unknown primary site of cancer [2]. Primary malignant brain tumors are responsible for over 15,000 deaths annually in the United States, with an annual incidence of 7 per 100,000 individuals [3]. The symptoms of malignant brain tumors are nonspecific and often include headaches (50%), seizures (20%-50%), cognitive decline (30%-40%), and focal neurological deficits (10%-40%) [3].

Over the past three years, the classification of central nervous system tumors has changed to include molecular profiling and immunophenotyping of the cells comprising them [4]. This change is due to the fact that the expression of certain markers determines the prognosis and survival of patients. According to the World Health Organization (WHO) classification of 2021, primary brain tumors is divided into the following categories: (1) Gliomas, glioma-neuronal, and neuronal tumors, (2) Tumors of the choroid plexus, (3) Embryonic tumors, (4) Tumors of the pineal region, (5) Intra-axial and non-meningothelial tumors, and (6) Tumors in the area of the pituitary[4].

In recent years, according to the Global Burden of Disease 2019 study database, brain tumors have been trending upwards, with mortality rates following a similar pattern. The clear cause of this increase has not yet been elucidated [5]. Some researchers implicate the aging population and the improved diagnostic accuracy of imaging and diagnostic methods [6], while others propose various acquired and environmental factors [7].

This study is the first research that has been conducted in Greece regarding the epidemiology of intracranial tumors in adults. We will present all the tumors that have been surgically treated at our clinic in the last two decades, from 2003 to 2023, along with the corresponding epidemiological analysis of these cases

MATERIALS AND METHODS

Over 1000 cases were operated on in our clinic from January 2003 to December 2023 due to space-occupying intracranial lesions. Among these, 823 histological reports were available, while the remaining cases were excluded from the study. Overall, there were 700 primary intracranial tumors and 123 secondary lesions. Additionally, one case involving a 4-year-old patient was excluded. The demographic data (age, gender and type of tumor) of the patients were also analyzed.

We divided all the tumors into seven categories: glioblastoma (GBM), meningioma, gliomas (excluding GMBs), pituitary tumors, central nervous system lymphomas, metastasis, and others. In the "other" category, the following lesions were included: epidermoid cyst, pineocytoma, neurocytoma, schwannoma/neurinoma, cerebellar hemangioblastoma, craniopharyngioma, colloid cyst, chondroma, ganglioglioma, ependymoma, choroid plexus papilloma, medulloblastoma, plasmacytoma, tumor of glial or neuronal origin, and non-diagnostic biopsies that indicated a primary brain tumor. We chose this classification because the histopathological reports did not follow the same WHO classification, as it has changed over time. Finally, we divided the histopathological reports into two decades, 2003-2012 and 2013-2023, and compared the frequency of each tumor category in each of these decades. The study was approved from the institutional review board.

RESULTS

Of the 823 patients with intracranial lesions who underwent surgery in our clinic and were included in the study, the average age was 56.6 years, with a range of 19 to 86 years, with 45,9% being females and 54,1% males (Figure 1). Among the tumors, the one with the highest incidence rate was meningioma (32,0%), followed by GBMs (24,0%) and metastasis (15,0%). Gliomas, other types of tumors, pituitary tumors, and central nervous system lymphomas accounted for 13,0%, 12,0%, 3,0% and 1,0%, respectively (Figure 2). If we include glioblastomas in the glioma category, according to the WHO classification, it is clear that gliomas are the most common tumor type, with a rate of 37.0%.

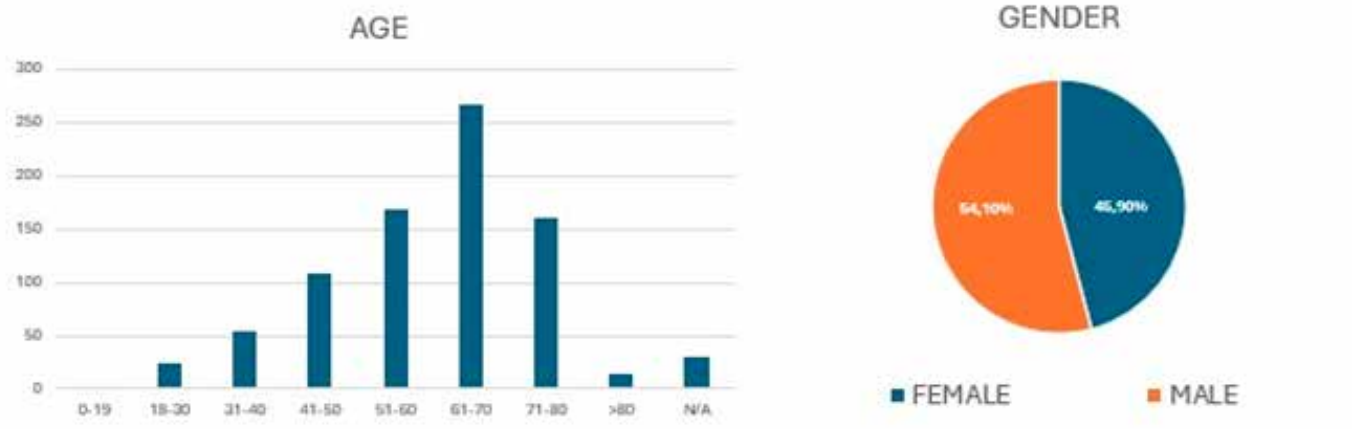


Figure 1. Demographic statistics (age and gender) of the patients.

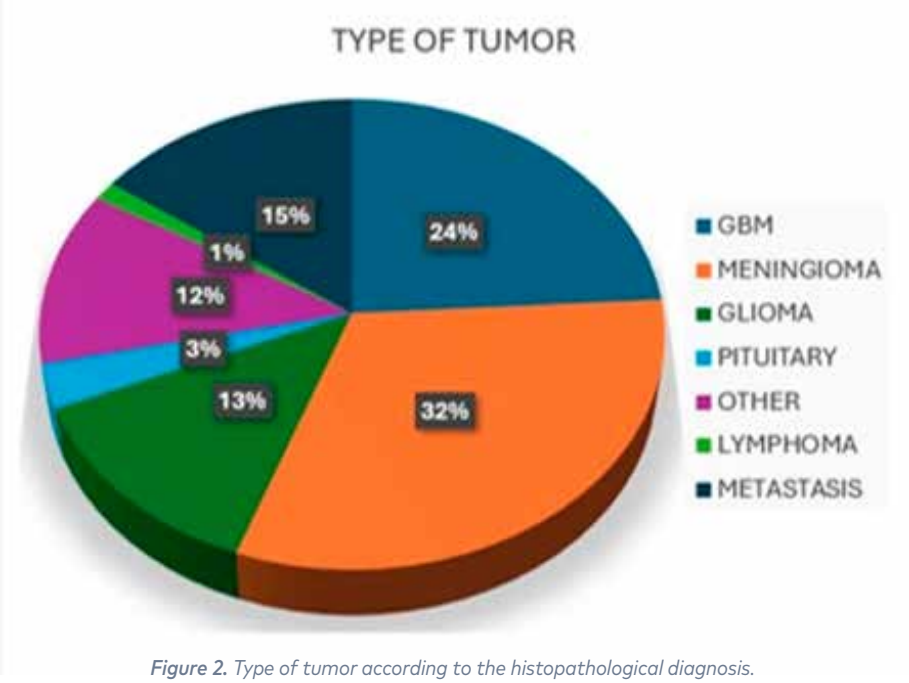


Figure 2. Type of tumor according to the histopathological diagnosis.

Within the primary intracranial tumors, the most common was the meningiomas accounted for 37,28%. The incidence of the other primary intracranial tumors were for GBMs 28,20%, for gliomas (excluding GBMs) 15,28%, for pituitary tumors 3,57%, for schwannomas 1,86%, for lymphomas 1,57%, for cerebellar hemangioblastomas 1,43%, for craniopharyngiomas 0,71%, for gangliogliomas 0,57%, for neurocytomas, primary melanoma, choroid plexus papilloma's, and epidermoid cysts 0,43% each and for tumors of glial or neuronal origin, ependymomas, chondromas, medulloblastomas, pineocytomas, plasmacytomas and colloid cysts for 0,14% each. Lastly, 6,57% of the biopsies indicated a primary brain tumor but the pathologists regarded samples as non-diagnostic. These results are depicted on Figure 3.

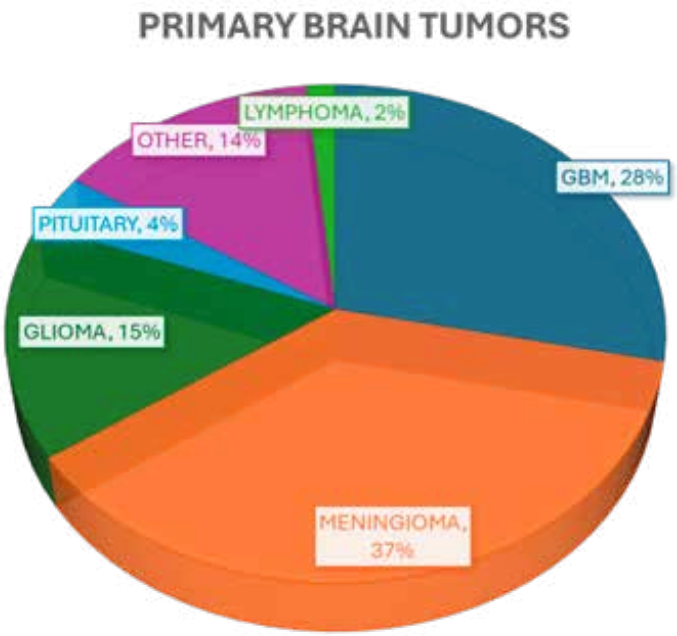


Figure 3. Type of primary brain tumors according to the histopathological diagnosis.

It is worth noting that the total number of gliomas increases to 42.56% with the addition of glioblastomas, making it clear that this is indeed the most common category of tumors. The histological type of the primary intracranial tumors, the number of cases, and the percentage of patients affected by each tumor type are presented in Table 1.

Table 1. Types of primary brain tumors.

Histologic type	n = 699	Precent
Meningiomas	261	37,28%
Glioblastoma	198	28,28%
Gliomas	107	15,28%
High grade tumors / No diagnostic biopsy	46	6,57%
Pituitary tumors	25	3,57%
Schwannoma-neurinoma	13	1,86%
Lymphomas	11	1,57%
Cerebellar hemangioblastoma	10	1,43%
Craniopharyngioma	5	0,71%
Ganglioglioma	4	0,57%
Neurocytoma	3	0,43%
Melanoma	3	0,43%
Choroid plexus papilloma	3	0,43%
Epidermoid cyst	2	0,43%
Ependymoma	1	0,14%
Cerebellar medulloblastoma	1	0,14%
Tumor of glial or neuronal origin	1	0,14%
Pineocytoma	1	0,14%
Colloid cyst	1	0,14%
Plasmacytoma	1	0,14%
Chondroma	1	0,14%
Gliosis	1	0,14%

As for the secondary tumors, their primary origins were from a wide variety of organs. The most frequent was the lung at 43,55%, followed by cancer of unknown primary origin (CUP) at 17,89%. The remaining origins were as follows: intestine 8,94%, melanoma 8,13%, breast 4,87%, urothelial epithelium 4,06%, stomach 3,25%, kidney, squamous cell cancer, and thyroid gland at 1.62% each. Finally, liver, prostate, lymphoma, and larynx accounted for 0.81% each. The primary origin of the secondary tumors, the number of cases, and the percentage of patients affected by each tumor type are presented in Table 2

Table 2. The primary origin of the secondary tumors.

Primary tumor	Metastasis n=123	Precent
Lung	54	43,55%
Cancer Unknown Primary	22	17,89%
Intestine	11	8,94%
Melanoma	10	8,13%
Breast	6	4,87%
Urothelial epithelium	5	4,06%
Stomach	4	3,25%
Kidney	2	1,62%
Squamous cell cancer	2	1,62%
Thyroid gland	2	1,62%
Liver	1	0,81%
Larynx	1	0,81%
Lymphoma	1	0,81%
Prostate	1	0,81%
Lung Or intestine	1	0,81%

Examining the tumors that were surgically treated between the two decades, there appear to be differences in the number of patients within each category of tumors. Over the last 2 decades the number of patients undergoing surgery for GBM increased, while on the contrary, those who underwent surgery for metastasis, lymphomas, meningiomas, gliomas (excluding GBMS), pituitary tumors, and other types of tumors, decreased. These results are presented in detail in Figure 4. Additionally, Figure 5 illustrate in detail the distribution of each tumor category each year from 2003 to 2023. The number of all cases that were operated on in our clinic between 2003-2012 and 2013-2023 seems to have slightly decreased, with 428 cases in the first decade and 395 in the second. Finally, if we include GBMs in the gliomas category, we will see that the number of patients increases from 114 to 159, indicating an overall increase in gliomas over the past decade (Figure 6).

Figure 4. Comparison between the two decades in every type of brain tumor.

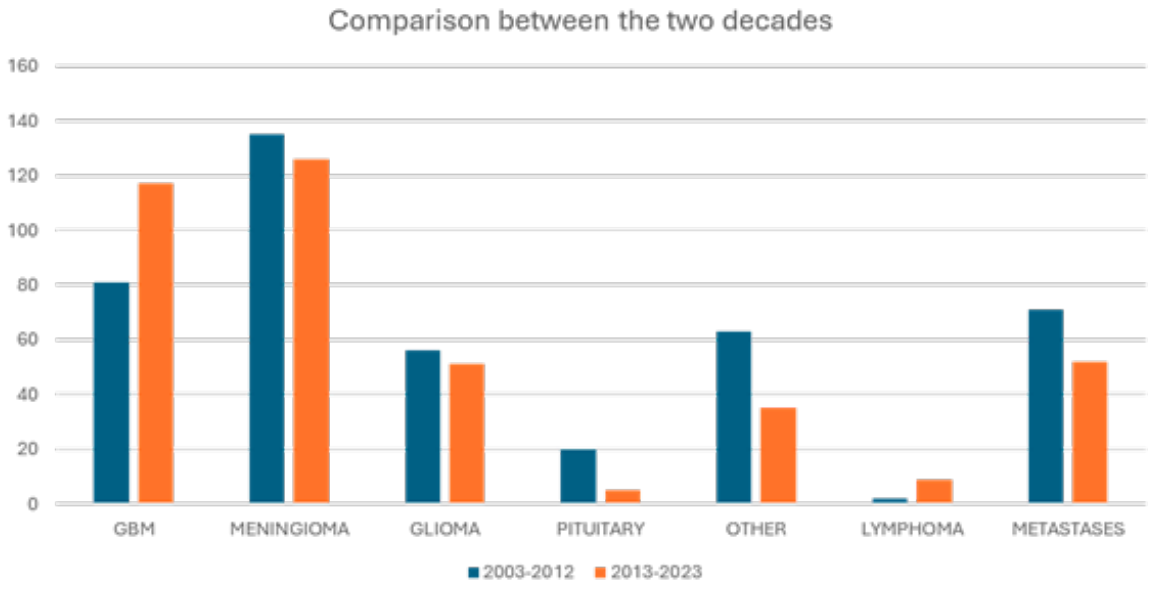


Figure 5. Number of each type of brain tumor in every year over the time from 2003-2023.

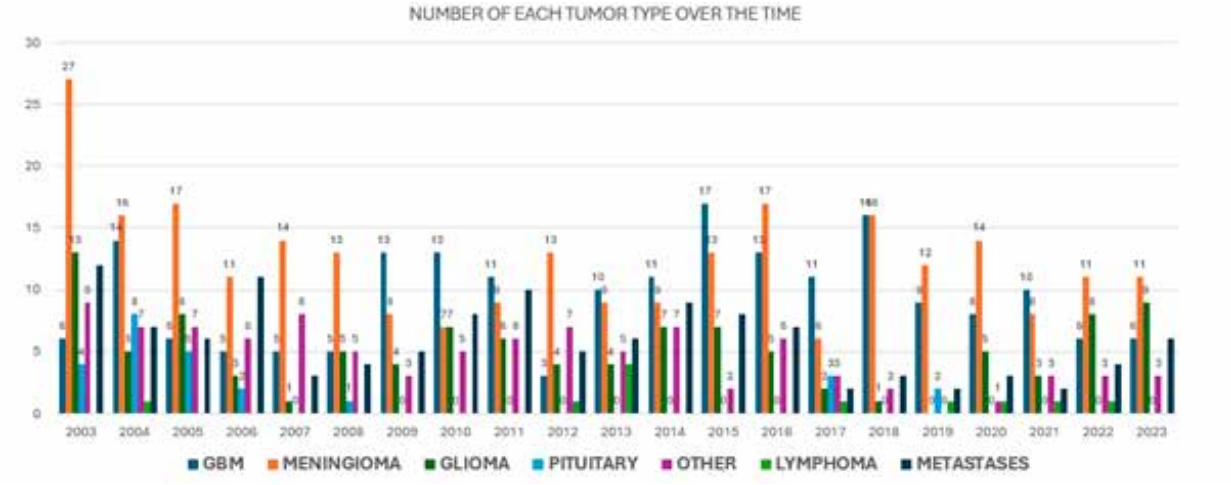
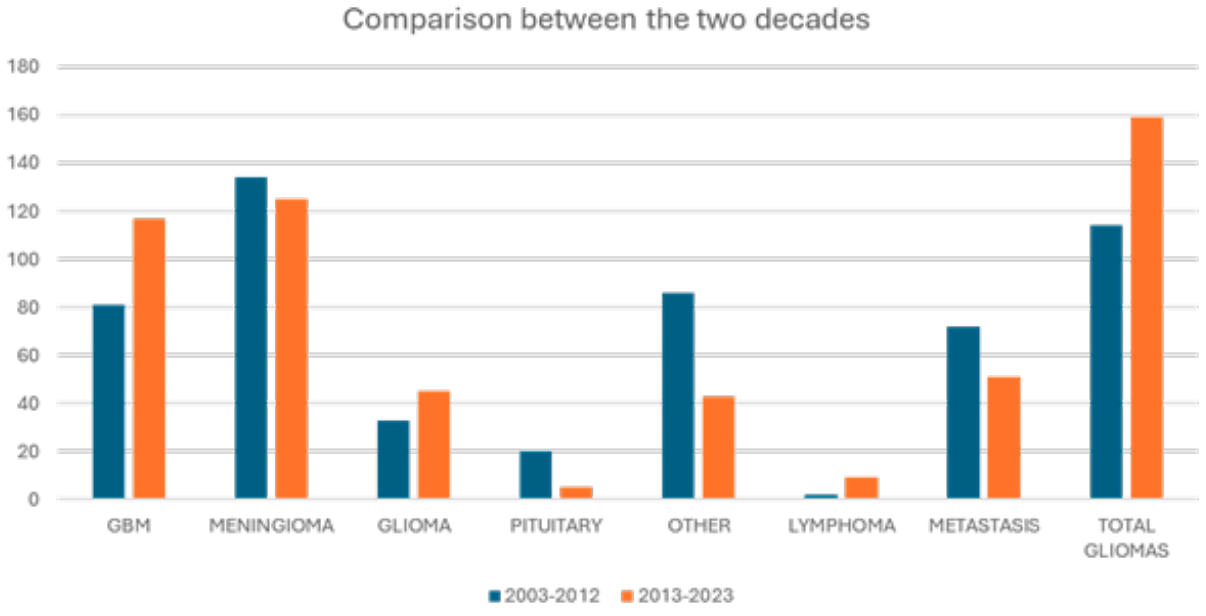


Figure 6. Comparison between the two decades in every type of brain tumor including the total number of gliomas.



DISCUSSION

Primary intracranial tumors are a relatively rare entity in adults, affecting less than 2% of the population [8]. However, they account for 13-20% of deaths due to malignant tumors in young adults and adults under 50 years old [9]. The high mortality rates are accompanied by high morbidity rates, leading to poor quality of life for patients suffering from this type of tumors [9]. On the other hand, brain metastases are much more common and are actually the most frequent intracranial tumors [10]. It has been proven that up to 26% of patients with cancer, who ultimately die from it, will develop one or more brain metastases at some point in their lives [1].

The epidemiology of primary brain tumors appears to change over time. According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute there was a total increase in the number of newly diagnosed brain tumors the last decades, despite the trend was descending during this decade [8]. On the other hand, data from Cancer Research UK indicates a dramatic increase in the incidence of the disease in the United Kingdom, with a 39% rise compared to the 1990s [11]. Similar results were presented in the systematic review published for the Global Burden of Disease Study, which highlighted that over the past three decades there has been an increase in the number of patients diagnosed with brain tumors [12]. In our study, we found that there was a decrease in the total number of patients who underwent surgery for a space-occupying lesion in the brain. This finding aligns with the SEER results for the last decade.

Among primary intracranial tumors, meningiomas are the most common tumor type, followed by gliomas, according to the Central Brain Tumor Registry of United States Statistical Report [13]. Among gliomas and malignant tumors, the most common was GBM, something also confirmed in our own results [13]. In our study we found that the most common category of tumors undergoing surgery was gliomas (47.56%), if we include GBMs and the second most common was meningiomas (37.28%). The difference in the percentages may be due to the fact that individuals with benign tumors such as meningiomas often choose not to undergo surgery, whereas patients with gliomas are more likely to undergo surgical intervention more readily and promptly.

Secondary brain tumors represent the most common type of brain tumor and are a devastating complication of primary malignancies, resulting in high rates of mortality and morbidity [14]. They are also 5-10 times more common than primary brain tumors, making them a major challenge for neurosurgeons, oncologists, and radiation therapists. The incidence of metastatic brain tumors appears to have increased in recent years according to the literature [15,16]. However, our study revealed a decrease in metastatic lesions undergoing surgery during the second decade. The reduction in the number of metastases may be attributed to the fact that these tumors can be treated using alternative methods now , and surgery is no longer the only option for these patients, unlike in previous years.

If we examine the tumor categories individually, we observe that the number of patients with glioblastomas and gliomas in general has increased over the past decade, while the number of cases with meningiomas has decreased according to our study results. In contrast to our findings, data from the SEER-9 program indicated that the incidence of gliomas appears to have stabilized over the past 20 years [17]. Especially for GBMs, another study conducted in Malta from 2008 to 2017 observed an increase in the incidence of the disease during this decade, which is in agreement with our own findings [18]. However, according to SEER-18 data the incidence of meningiomas appears to have increased over the past 20 years during the initial years and then remained stable thereafter [19]. The different results between our study and the literature may be attributed to our smaller sample size, different population demographics, and inclusion of only surgically treated cases, whereas the literature includes all diagnosed cases. Moreover, most of the pituitary tumors are no longer operated on in our department and that there was a period from 2019 to 2022 when the number of cases was limited due to the Covid-19 pandemic.

As for the secondary brain tumors we find that the most common primary site was the lung followed by CUP, the intestine, melanoma, breast and others. According to the literature, the most common secondary brain tumor is lung cancer, which is explained by the increased incidence of this disease [20-22]. This finding is consistent with the results of our study. Breast cancer appears to have the second highest frequency, followed by melanoma, kidney cancer, and CUP [20-23]. Our results seem to differ from the literature, which may primarily be due to the fact that the number of patients included in our study only involved cases that underwent surgery. Additionally, demographic characteristics can vary from region to region within a country.

At the moment, there are no epidemiological studies regarding brain tumors in our country, except for one study focusing solely on the pediatric population from a single center [24]. Although there are databases with epidemiological data on brain tumors, such as those from the SEER program [8], it is unclear how applicable they are to our population. Our study is unique in our country but has limitations due to its small sample size and the fact that our hospital is small, which may not represent all cases in our country. A larger, multi-institutional study on the epidemiology of brain tumors in the adult population of our country is deemed necessary to draw more accurate conclusions about the incidence of brain tumors here.

Limitations

First of all, the number of cases included in the study was very small and pertained to only a small area of our country, so the results may not be representative of the entire country. Additionally, the study was retrospective, and many cases were excluded because there was no final histological biopsy to confirm the tumor. Finally, our results include only cases that underwent surgery, not all cases that were diagnosed with brain tumors in our hospital. For this reason, the comparisons made with the literature are not entirely representative of the total number of patients who presented to our clinic due to an intracranial malignancy.

CONCLUSIONS

Concluding, our study on the epidemiology of brain tumors from 2003 to 2023 in the adult population of Greece represents the first extensive research of its kind in our country. From the results, we observed a slight decrease in the overall number of cases over the last decade compared to the previous one. However, there was an increase in the number of patients undergoing surgery for gliomas, particularly glioblastomas. This observation may indicate an increase in the incidence of the disease in our region. These findings warrant further investigation and a larger multicenter study involving more hospitals across Greece to provide a more comprehensive picture of the epidemiology of brain tumors in our country.

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None

CONFLICT OF INTEREST

None

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None

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CASE REPORT

Human pseudo-tail associated with dermal sinus tract and tethered cord

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ABSTRACT

Introduction: Pseudo-tails are frequently linked with occult spinal dysraphism. We present a peculiar case of a lumbosacral pseudo-tail in a male newborn associated with a congenital dermal sinus. which later developed tethered cord that required surgery.

Case presentation: A 2.2 kg male baby was born at 39 weeks of gestation. Clinical examination revealed a soft, skin covered protrusion located just right of the midline, near the lumbosacral junction, resembling a human tail. Magnetic resonance imaging (MRI) of the spine identified a dermal sinus tract continuous with the dermal appendage. At 3 months of age, surgery was performed under general anesthesia where the tract was explored and removed. After the age of 3, the parents noticed that he was unable to walk at a fast pace and run. A repeat MRI of the spine showed spinal dysraphism in the form of spina bifida at S1 and low-lying tethered spinal cord. A second operation was performed where the dura was opened and detethering of filum terminale was done under the microscope. The child recovered well after surgery with no complications. Postoperative MRI at 18 months confirmed the release of filum terminale. At the last follow -up. his neurological status was normal and he was able to walk and run without any difficulty.

Conclusions: Human tails are often associated with spinal dysraphism and other lesions which should be operated, if indicated. Long-term surveillance is also highly recommended to detect and prevent progressive neurological deficits.

Keywords: Pseudo-tail, Dermal Sinus Tract, Tethered Cord, Surgical treatment

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Οι ψευδοουρές συνδέονται συχνά με την παρουσία λανθάνουσας δισχιδούς ράχης στη σπονδυλική στήλη. Παρουσιάζεται μια περίπτωση ψευδοουράς στην οσφυοϊερή μοίρα σε άρρεν νεογέννητο που σχετιζόταν με συγγενή δερματικό πόρο και αργότερα ανέπτυξε καθήλωση του τελικού νηματίου.

Παρουσίαση περιστατικού: Άρρην νεογνό 2,2 κιλών γεννήθηκε στις 39 εβδομάδες κύησης. Η κλινική εξέταση αποκάλυψε μια μαλακή, καλυμμένη με το δέρμα προεξοχή ακριβώς δεξιά από τη μέση γραμμή, κοντά στην οσφυοϊερή συμβολή, που ομοίαζε με ανθρώπινη ουρά. Η μαγνητική τομογραφία (MRI) της σπονδυλικής στήλης εντόπισε την παρουσία δερματικού πόρου σε συνέχεια με τη δερματική αλλοίωση. Σε ηλικία 3 μηνών, έγινε χειρουργική επέμβαση διερεύνησης και αφαίρεσης του πόρου. Μετά την ηλικία των 3 ετών, οι γονείς παρατήρησαν ότι το παιδί δεν μπορούσε να περπατήσει με γρήγορο ρυθμό ούτε και να τρέξει. Η μαγνητική τομογραφία της σπονδυλικής στήλης έδειξε καθηλωμένο τελικό νημάτιο. Πραγματοποιήθηκε δεύτερη επέμβαση όπου η μήνιγγα ανοίχτηκε και ακολούθησε η διατομή του τελικού νηματίου και η απελευθέρωση της καθήλωσης κάτω από το μικροσκόπιο. Το παιδί ανάρρωσε καλά μετά την επέμβαση χωρίς επιπλοκές. Η μετεγχειρητική μαγνητική τομογραφία στους 18 μήνες επιβεβαίωσε την κατάσταση του τελικού νηματίου μετά το χειρουργείο. Στην τελευταία κλινική εκτίμηση, η νευρολογική του κατάσταση ήταν φυσιολογική. Μπορούσε να περπατήσει, αλλά και να τρέξει χωρίς δυσκολία. Θα συνεχίσει να παρακολουθείται για το ενδεχόμενο επανακαθήλωσης του τελικού νηματίου, αλλά και εμφάνισης ορθοκυστικών διαταραχών.

Συμπεράσματα: Οι ανθρώπινες ουρές συχνά συνδέονται με δισχιδή ράχη, αλλά και με άλλες βλάβες. Σε περίπτωση που προκαλούν συμπτώματα, θα πρέπει να χειρουργούνται κάτω από συγκεκριμένες ενδείξεις, Συνιστάται η μακροχρόνια παρακολούθηση ιδιαίτερα για τον εντοπισμό και την πρόληψη νευρολογικών διαταραχών.

Λέξεις κλειδιά: Ψευρο-ουρά, Συγγενής δερματικός πόρος καθηλωμένη τελικό νημάτιο, χειρουργική αντιμετώπιση.

INTRODUCTION

Skin covered appendages of the lumbosacrococcygeal region considered human-tails are rare malformations [1]. True-tails are benign lesions independent from spinal cord or cauda equina, whereas pseudo-tails are highly associated with occult spinal dysraphism [2]. Dermal sinus tracts are also uncommon and extend from the skin to deeper and variable structures [3]. Assessment must include complete neurological history and examination as well as detailed radiological workup [1].

We present a peculiar case of a lumbosacral pseudo-tail in a male newborn associated with a congenital dermal sinus which later developed tethered cord that required surgery.

CASE PRESENTATION

A 2,220 kg male was born by vaginal delivery at 37 weeks of gestation. Clinical examination revealed a soft, skin covered protrusion approximately 1.5 cm in length and 0.5 cm in diameter, located just right of the midline, near the lumbosacral junction, resembling a human tail (Figure 1). The neurological examination was normal.

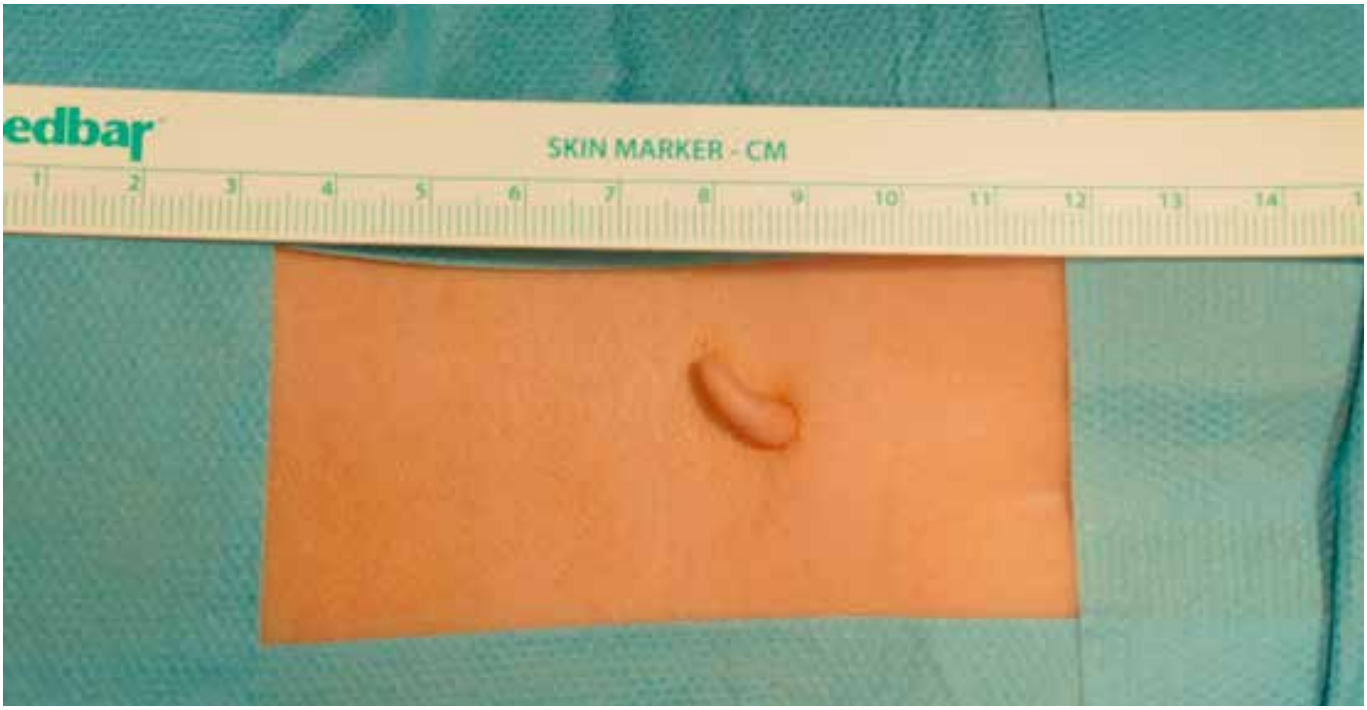


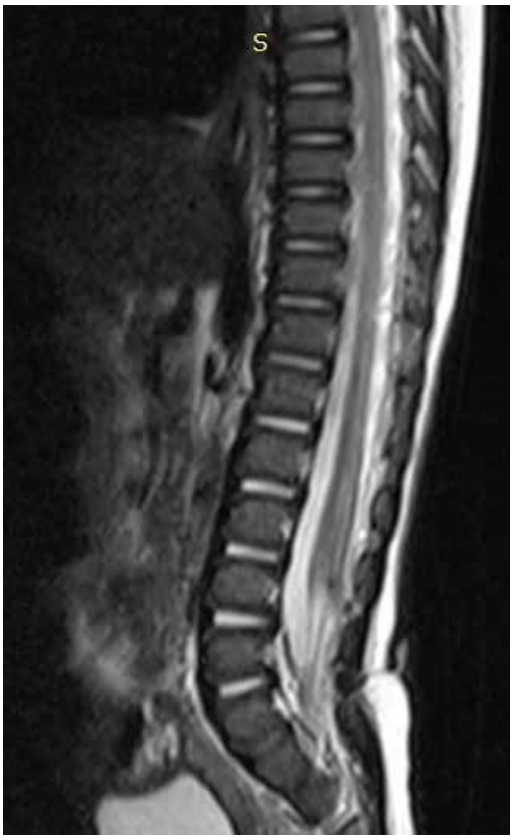
Figure 1. The pseudo-tail before surgical excision.

Magnetic resonance imaging (MRI) of the spine identified a dermal sinus tract continuous with the dermal appendage, extending from the thecal sac to the spinal canal and terminating at the dura mater at the L5-S1 level. No spinal cord tethering was initially detected (Figure 2).

At 3 months of age, surgery was performed under general anesthesia. During surgery the pseudo-tail was removed and the dermal sinus was ligated just over the dura through a vertical incision encircling the base of appendage. Histopathological examination confirmed the presence of dermal sinus tract as well as findings indicative of a fibrous hamartoma of infancy. The postoperative period was uneventful. After discharge, he was followed closely by the pediatricians and neurosurgeons retaining a normal neurological status at 6, 12 and 24 months of follow-up.

After the age of 3, his parents noticed that he was unable to walk at a fast pace and run. A repeat MRI of the spine showed spinal dysraphism in the form of spina bifida at S1 and low-lying tethered spinal cord (Figure 3).

Figure 1. Magnetic Resonance Imaging (MRI) of the spine after birth showing the dermal sinus tract..



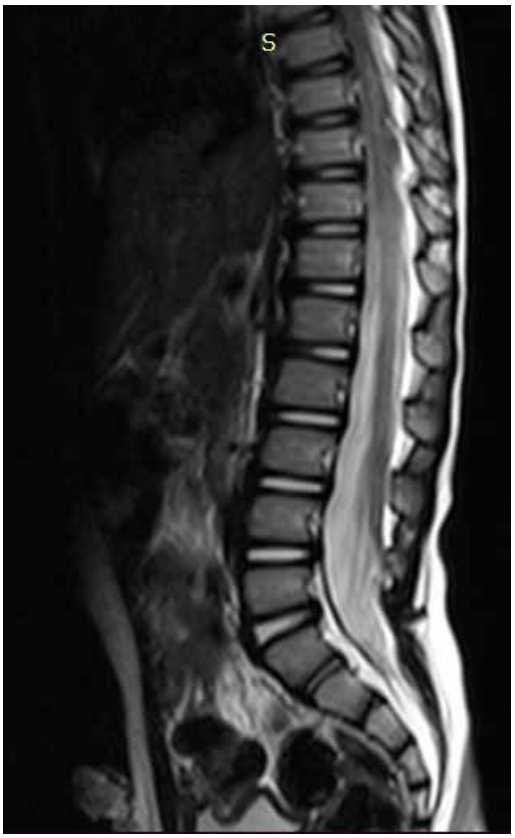


Figure 3. Magnetic Resonance Imaging (MRI) of the spine after birth showing the dermal sinus tract..

A second operation was performed where the dura was opened and detethering of filum terminale was done under the microscope. The dura was closed watertight using microsurgical techniques. The child recovered well after surgery with no complications. Postoperative MRI at 18 months confirmed the adequate release of filum terminale. At last follow-up his neurological status was normal and he was able to walk and run without any difficulty. Nevertheless, mild bladder problems in the form of urinary bladder distention were recorded which are under investigation.

DISCUSSION

According to Dao and Netsky, some features can distinguish true tails from pseudo-tails. A true human tail is the distal, dermal-covered, midline protrusion which is a remnant of the unvertebrated embryonic tail, developed between the fourth and eighth week of fetal development. It contains adipose and connective tissue, striated muscle with ganglion cells, blood vessels and nerve fibers. True vestigial tails are not benign abnormalities and may be associated with underlying dysraphic state. On the other hand, the pseudo-tail is a secondary lumbosacral, mobile protrusion caused by anomalous prolongation of vertebrae, lipoma, teratoma or glioma and is often associated with occult spinal anomalies [4].

Spinal dysraphism and tethered cord have a reported association with human tails at 49% and 20%, respectively [2]. Review of the literature showed spina bifida to be the commonest co-existing abnormality [5]. In the current case, MRI showed a congenital dermal sinus tract extending from the appendage to the spinal canal at the L5-S1 level. Of note, the association of pseudo-tail with dermal sinus tract is uncommon compared to other forms of dysraphic state [3, 6, 7] (Table 1).

AUTHORS	YEAR	TITLE	FINDINGS
Chakrabortty et al.	1993	Myelomeningocele and thick filum terminale with tethered cord appearing as a human tail. Case report	Spina bifida: most frequent coexisting anomaly with human tail
Hoffman et al.	1985	Managementoflipomyelomeningoceles. Experience at the Hospital for Sick Children, Toronto	Fatty mass in the lumbosacral region was the most common presenting complaint in a series of 97 patients (5 of them presented with tail-like caudal appendages)
Lu et al.	1998	The human tail	Of the 59 cases with caudal appendages, 50% were associated with either meningocele or spina bifida occulta
McLone et Naidich	1985	Terminal myelocystocele	Of 48 skin-covered lumbosacral masses, 67% were lipomas and lipomyelomeningocele, 25% teratomas, 4% meningocele and 4% terminal myelocystoceles
Tavafoghi et al.	1978	Cutaneous signs of spinal dysraphism. Report of a patient with a tail-like lipoma and review of 200 cases in the literature	Cutaneous signs in more than 50% of instances with occult spinal dysraphism

Table 1. Cases of human tail associated with spinal dysraphism reported in the literature.

Skin lesions, such as caudal appendages, associated with spinal dysraphism are a well documented finding [8, 9]. Therefore, management of any true tail or pseudo-tail should include a thorough neurological examination and imaging studies of the vertebral column with computed tomography and/or MRI for evaluation of possible spinal anomaly [1].

In the past, plain radiographs were the only available tool [2]. Recently, computed tomography (CT) and MRI have revealed more detailed information about the associated defects (meningocele, myelomeningocele, lipomas, teratomas, tethered spinal cord etc) [1]. The optimal modality, however, for examining the caudal appendage and its internal surroundings is MRI, especially at the area between the lower thoracic vertebrae and the coccyx [2].

These patients require close follow-up to detect the development of tethered cord and prevent progression of neurological symptoms. Therefore, imaging at least at an annual basis is essential [2]. In the present case, the patient developed symptoms related to tethered cord some years later, although living a normal life. Despite an unremarkable neurological examination and a normal x-ray of the spine, a spinal MRI should always be performed and carefully interpreted [1]. Bladder problems are common in cases of spinal cord tethering and are not easy to handle [10].

When a human tail is identified, a thorough clinical and radiological examination is mandatory since its innocent-looking appearance may prompt the surgeon to perform only a superficial excision of the malformation [8]. However, special attention is required to deal with co-existing abnormalities as well [11]. Primary and most common treatment method for removing caudal appendages is surgery [12]. In cases of tails without interior connection, a simple excision is usually feasible. When an accompanying spinal dysraphism is diagnosed, neurosurgical intervention is suggested [12]. Urgency depends on the abnormality and the presenting clinical symptoms. In more serious cases, such as symptomatic tethering of the spinal cord, microsurgery with untethering should be performed as early as possible, ideally before 2 years of age, to avoid future neurological deficits and disability [2].

CONCLUSION

Human tail is a rare anomaly. It should be carefully investigated and closely monitored, because it is often associated with spinal dysraphism and other lesions. Treatment should be done the earliest possible. Long-term surveillance is also highly recommended to detect and prevent progressive neurological deficits especially in the presence of progressive spinal cord tethering.

PATIENT CONSENT

Written informed consent was obtained from the patient.

CONFLICT OF INTEREST

None

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CASE REPORT

Onyx embolization of an unruptured brain arteriovenous malformation

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ABSTRACT
Brain arteriovenous malformations (bAVMs) are relatively rare congenital lesions characterized by high blood flow through an abnormal arteriovenous shunt. Despite recent advances, management of bAVMs - especially unruptured ones - remains controversial. We present the case of a 22-year-old man with a right sided 3cm temporal bAVM incidentally identified after a road traffic accident. The lesion was treated with a combination of endovascular embolization and radiosurgery. Technical details of the case as well as the natural history and treatment algorithms for the disease are discussed. Neurosurgeons need to be aware that the complexity of bAVMs calls for special consideration and decisions should always be made on a multidisciplinary team basis.

KEYWORDS
AVM, Cerebral vascular malformations, Embolization, Onyx Embolization.

ΠΕΡΙΛΗΨΗ
Οι αρτηριοφλεβώδεις δυσπλασίες του εγκεφάλου (ΑΦΔ) είναι σχετικά σπάνιες συγγενείς βλάβες που χαρακτηρίζονται από υψηλή ροή αίματος μέσω μιας ανώμαλης αρτηριοφλεβικής ροής. Παρά τις πρόσφατες εξελίξεις, η διαχείριση των ΑΦΔ - ειδικά αυτών που δεν έχουν υποστεί ρήξη - παραμένει αμφιλεγόμενη. Παρουσιάζουμε την περίπτωση ενός 22χρονου άνδρα με δεξιά κροταφική ΑΦΔ, 3 cm, που εντοπίστηκε τυχαία μετά από τροχαίο ατύχημα. Η βλάβη αντιμετωπίστηκε με συνδυασμό ενδοαγγειακού εμβολισμού και ακτινοχειρουργικής. Συζητούνται οι τεχνικές λεπτομέρειες, η φυσική εξέλιξη και ο αλγόριθμος θεραπείας. Οι νευροχειρουργοί πρέπει να γνωρίζουν ότι η πολυπλοκότητα των εγκεφαλικών ΑΦΔ απαιτεί ιδιαίτερη προσοχή και το θεραπευτικό πλάνο πρέπει πάντα να καταρτίζεται από μια διεπιστημονική ομάδα.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ
Αρτηριοφλεβώδης δυσπλασία, εμβολισμός, Onyx.

INTRODUCTION

Brain arteriovenous malformations (bAVMs) are relatively rare congenital lesions characterized by high blood flow through an abnormal arteriovenous shunt. Despite recent advances, management of bAVMs - especially unruptured ones - remains controversial. Decision making is primarily based on the mode of presentation and the angioarchitecture of a given lesion but other factors (e.g. patient's age and comorbidities) need to be taken into consideration as well. Our case is that of an unruptured right sided 3cm temporal bAVM which was treated with a combination of endovascular embolization and radiosurgery.

CASE DESCRIPTION

A 22-year-old man was referred to our hospital due to a bAVM incidentally identified on cranial imaging after a road traffic accident (Figure 1 - 3). The patient's neurological examination was completely normal and he denied symptoms that could be in any way related to the lesion (seizures, headaches etc). His past medical history was unremarkable and he reported no use of medications or other substances.

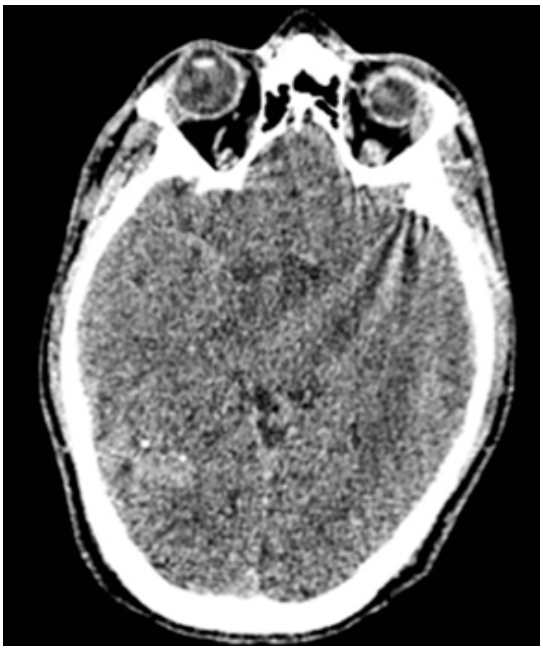


Figure 1. Unenhanced axial CT scans revealing a right temporal lobe lesion reported as a brain AVM. A focal area of calcification can be seen on the anterior aspect of the lesion.

Figure 2. Axial T2 (Left) and sagittal T1 (Right) weighted MRI images confirming the presence of a right posterior temporal lobe AVM. Note the presence of two large intranidal venous varices.

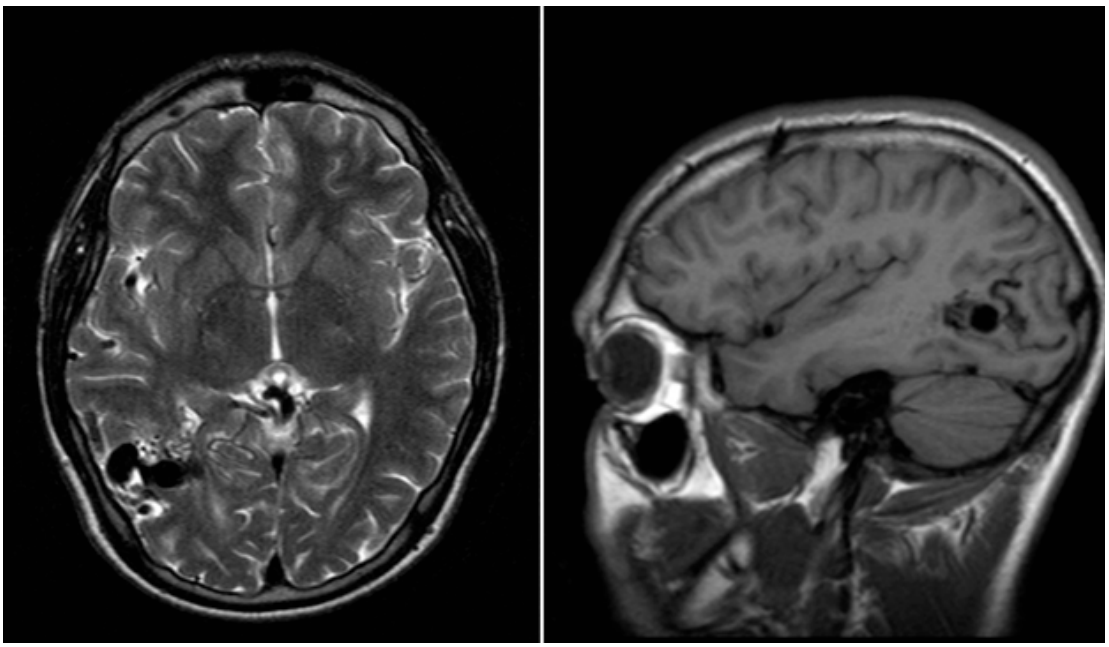
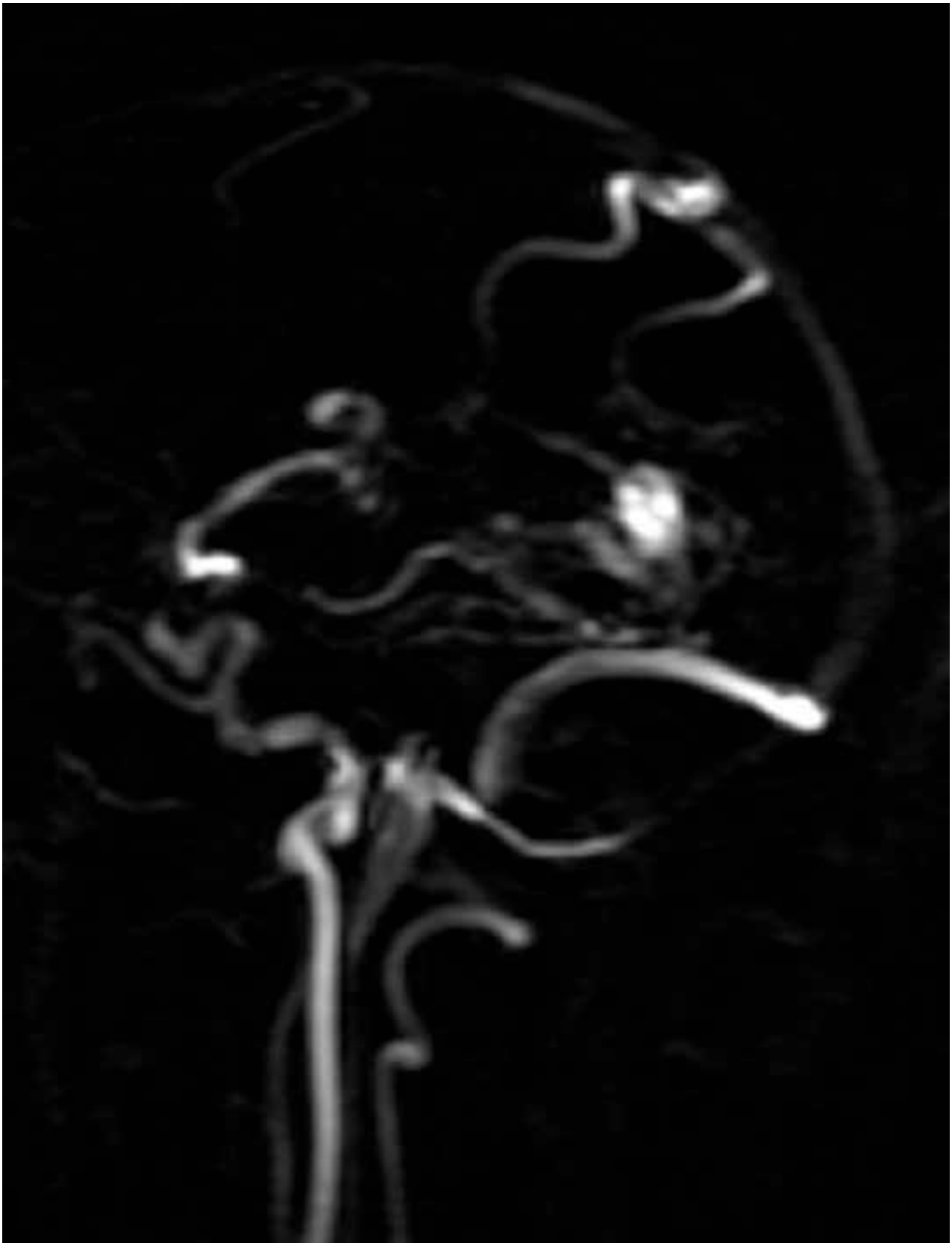
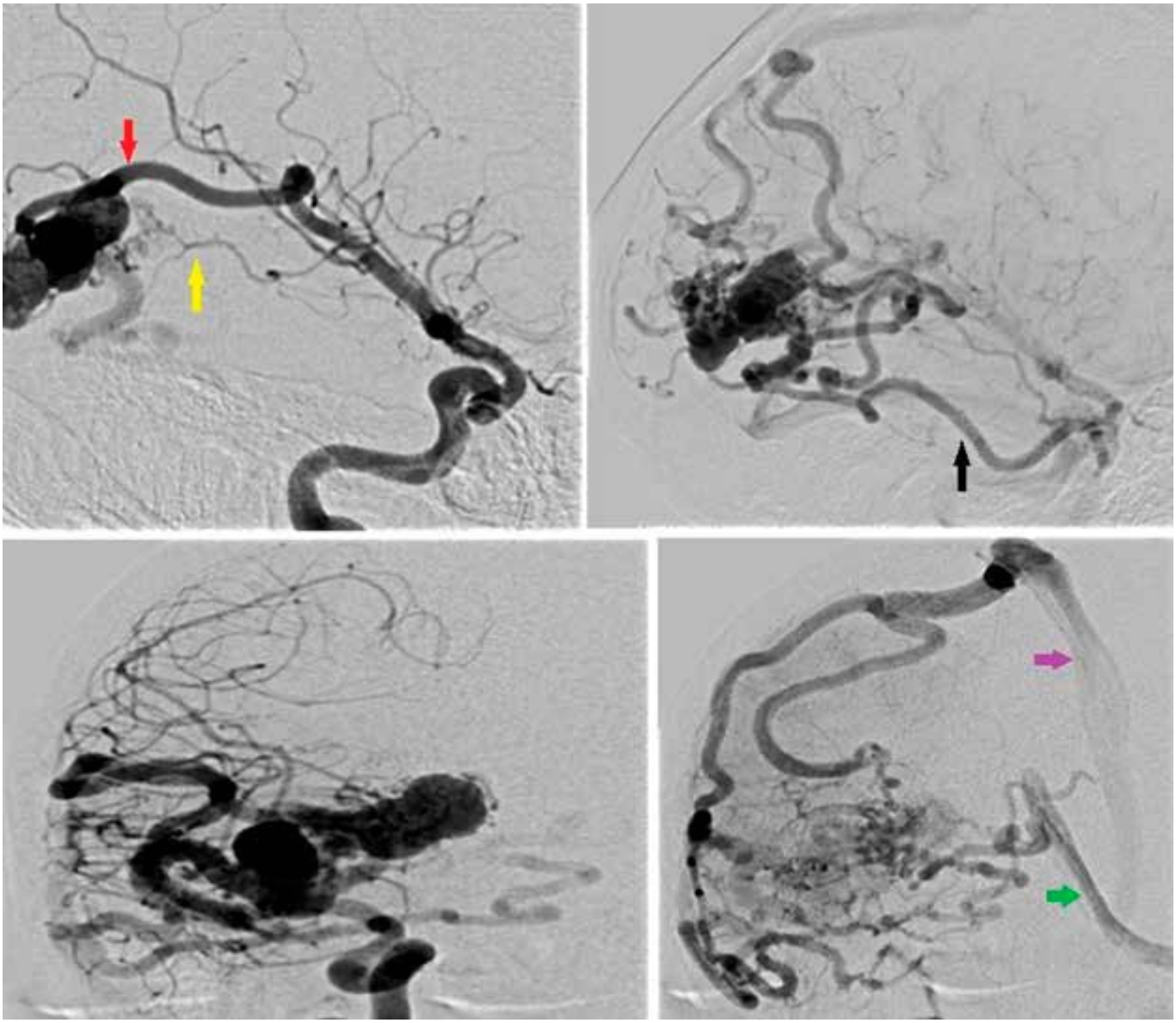


Figure 3. Reconstructed MRA image showing the temporal bAVM.



As part of the patient's initial evaluation, a DSA was performed to further investigate the malformation in hand and its angioarchitecture (Fig. 4). Images confirmed our previous findings. The AVM had a 3cm compact nidus and was situated on the right posterior temporal lobe. Arterial supply was mainly through the temporo-occipital branch of the MCA. A secondary proximal MCA feeder could also be identified. Drainage was through large tortuous veins running into the straight, the cavernous and the superior sagittal sinuses. No intranidal or other flow related aneurysm could be seen.

Figure 4. (Top) Initial DSA, lateral view. Temporal AVM supplied by the MCA (yellow and red arrows) with the main feeder (red arrow) being its temporo-occipital branch. Drainage is through tortuous veins running into the superior sagittal, the cavernous (black arrow) and the straight sinuses. No ECA involvement was noted. No flow related aneurysm was identified. Note the formation of two large intranidal venous varices. (Bottom) Initial DSA, lateral AP view. Descriptions as above. The purple arrow shows the superior saggital sinus and the green arrow the straight sinus.



After detailed discussion of these findings in an MDT meeting with the neurosurgical team, the malformation was classified as a Spetzler-Martin Grade II AVM and a combination of stereotactic radiosurgery plus embolization was proposed to the patient. The aim of the endovascular treatment would be, in this context, to reduce both the size and the flow of the AVM, facilitating subsequent complete obliteration through γ-knife.

The endovascular procedure was performed under general anaesthesia. A 6F sheath was placed in the right common femoral artery and a 6F Envoy guider was used to selectively catheterize the right ICA. Using roadmap, and over a Traxcess 14 guide wire, two microcatheters, an Echelon 10 and - subsequently - a Marathon, were navigated close to the nidus and past the last cortical branch of the AVM's main arterial feeder (Figure 5 & 6).

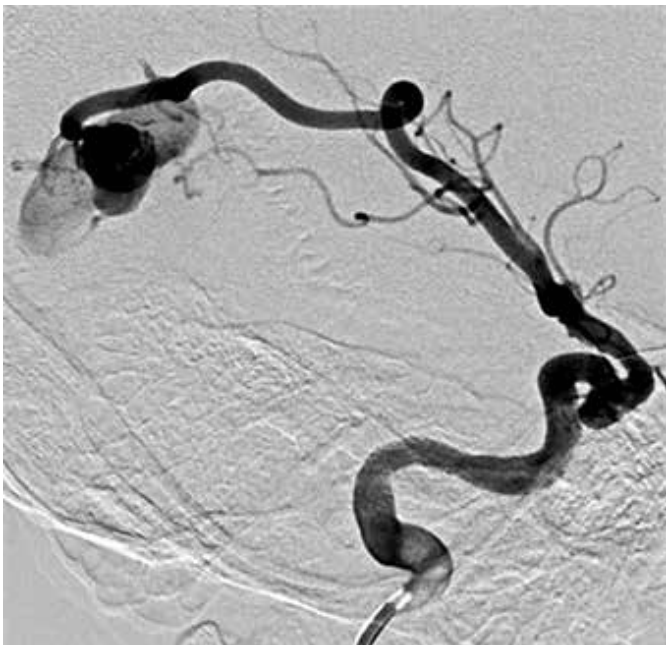


Figure 5. Embolization procedure. Right ICA injection, working projections (lateral view).

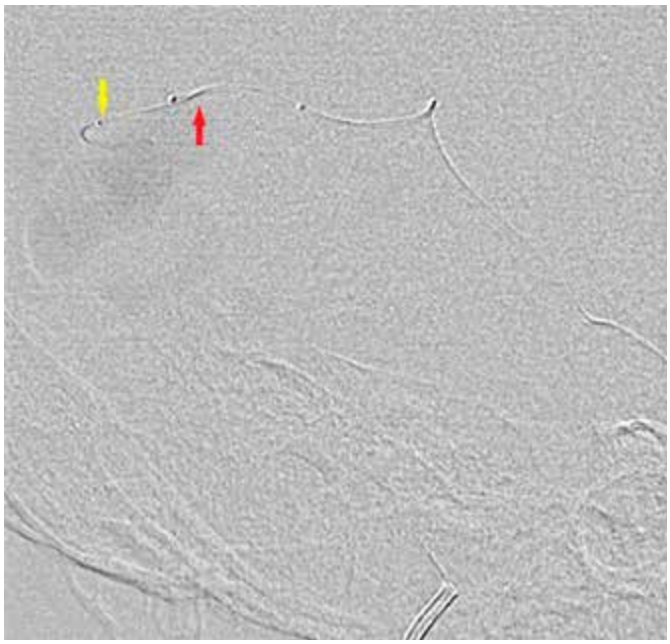


Figure 6. Embolization procedure. The Echelon and Marathon microcatheters were navigated close to the AVM nidus over a Traxcess 14 guidewire (Echelon – red arrow, Marathon – yellow arrow).

Using the Echelon microcatheter, a 4mm X 10cm OrbitGalaxy G2 coil was deployed within the feeding artery to reduce blood flow and provide a scaffold for the Onyx injection (Figure 7). In total, 2.71 mls of Onyx 18 were injected through the Marathon microcatheter and over 30 minutes, partially occluding the AVM nidus and significantly reducing the shunt (Figure 8). A final angiogram confirmed a satisfactory haemodynamic result and the procedure was terminated (Figure 9). Haemostasis was achieved with the aid of a 6F AngioSeal device. The patient awoke in the angio suite with no new neurological deficits and he was later on discharged home with a plan for a repeat angio in 3 months.

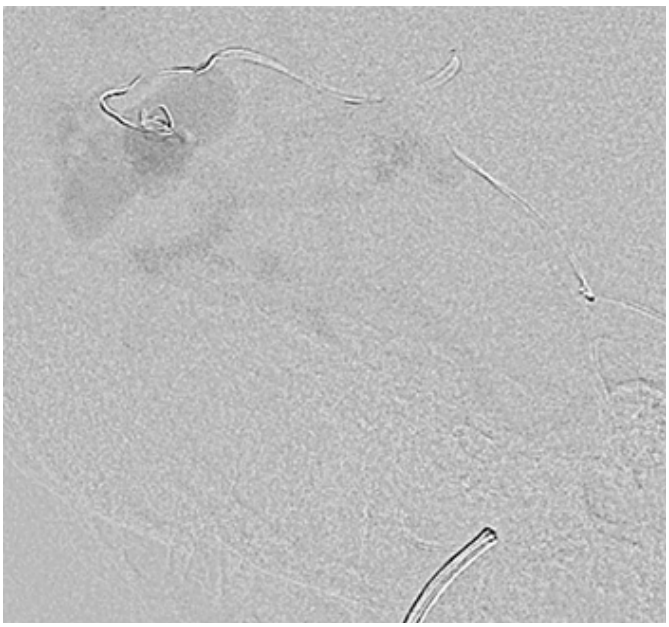


Figure 7. Embolization procedure. Deployment of the coil through the Echelon microcatheter.

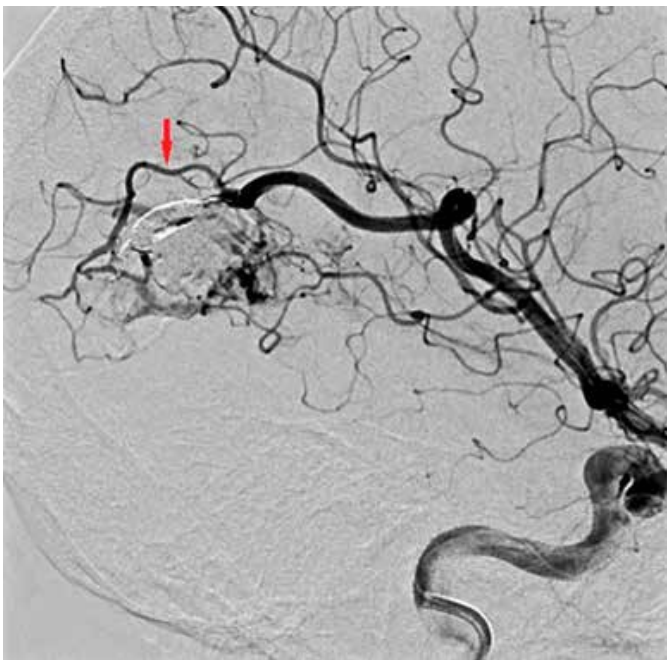


Figure 8. Embolization procedure. Onyx injections. Despite reflux, preservation of a cortical vessel branching off the AVM's main arterial feeder (red arrow).

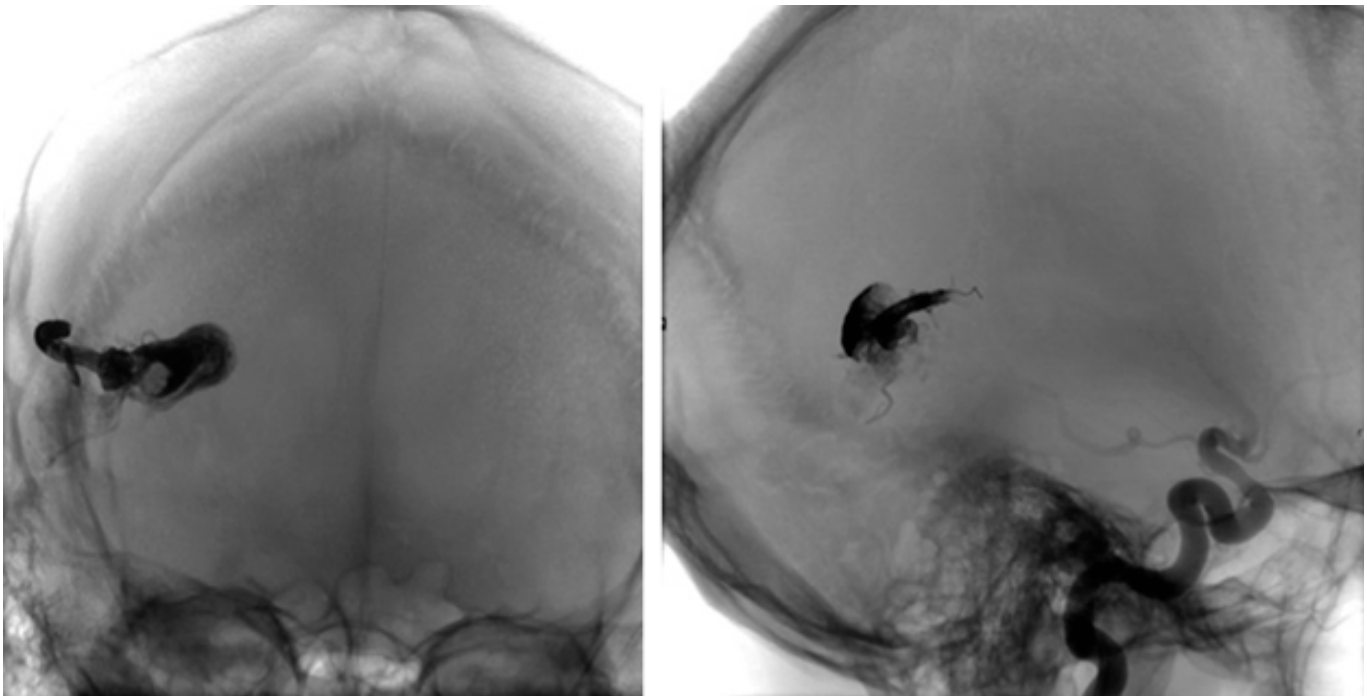


Figure 9. Onyx cast AP (Left) and lateral (Right) views.

DISCUSSION

As already mentioned, bAVMs are relatively rare congenital lesions characterized by high blood flow through an abnormal arteriovenous shunt. Typically, feeding arteries of a bAVM connect to a network of poorly differentiated, immature and structurally ambiguous vessels (nidus). Oxygenated blood rushes through them directly into the venous system, without any gas exchange occurring in a capillary bed (i.e. non-nutritional flow). In rare occasions (<2%), bAVMs may take the form of a direct communication between an enlarged artery and a vein with no interposed nidus (fistulous AVMs) [1].

Most bAVMs remain silent throughout life and only 12% of cases become symptomatic [2]. Common presentations include haemorrhage (50%), seizures (30%) and headaches (15%) (Mast, 1995). AVM associated focal neurological deficits are caused by either mass effect or steal phenomena. Rare forms of presentation include dilated facial and scalp veins, heart failure (infants) and obstructive hydrocephalus (enlarged vein of Galen as a channel for AVM drainage) [3].

Despite recent advances in disease understanding, management of bAVMs remains controversial. In general, treatment is offered in all patients with an AVM related haemorrhage as well as young patients with one or more risk factors for AVM rupture. Given that surgery still presents today as the mainstay treatment, the risk of surgical morbidity and mortality associated with a given lesion needs also to be considered. Facilitating decision making, the Spetzler-Martin AVM classification system grades lesions according to their surgical difficulty and taking into account their size, location and pattern of venous drainage [4]. Based on the Spetzler-Martin scheme, AVM management guidelines have been produced and published by the American Heart Association in 2001 [5]:

Grade I and II lesions

First line treatment for low grade lesions is surgery. Preoperative embolization to obliterate inaccessible arterial feeders is an option, it should be instituted though no more than a week prior to the main procedure to avoid re-growth of deep perforators. Radiosurgery should be reserved for selected cases (e.g., patients with comorbidities, deep lesions or lesions involving eloquent areas).

Grade III lesions

Treatment should be through a combination of embolization and surgery or radiosurgery. Pre-surgical embolization improves outcome by (1) eliminating deep or surgically inaccessible feeders, (2) decreasing the nidus size (shorter surgical times and less blood loss), (3) providing a «road map» for the surgeon (embolized vessels are easier to identify intraoperatively), (4) preventing normal perfusion pressure breakthrough (staged therapy) and (5) eliminating angioarchitectural characteristics associated with increased risk of intraoperative haemorrhage (intranidal or other flow related aneurysms). Pre-radiosurgical embolization facilitates γ-knife by shrinking the nidus (<3cm or <10cm3) and occluding high flow fistulas that can be refractory to radiation treatment. It also obliterates AVM related aneurysms that represent a risk factor for haemorrhage during the radiation latent period (up to 3 years). Note that, in a recent study, risk of permanent morbidity and mortality after AVM embolization with Onyx was 5% and 2% respectively [6].

Grade IV and V lesions

High grade lesions are regarded as incurable and, unless a patient has repeated haemorrhages or progressive neurological deficits, conservative management seems to be the first option. Should treatment be needed, this is on a case by case basis and through a multimodality approach. It should be mentioned here that partial obliteration of an

AVM does not protect from haemorrhage and may even worsen the clinical course of the lesion. Nevertheless, for incurable AVMs, targeted or palliative embolization to lower rupture risk or ease symptoms respectively are viable options. An alternative is staged radiosurgery.

CONCLUSION

Management of brain AVMs has always been a challenge for physicians. Despite recent advances, today's trend seems to move away from aggressive treatment and towards a more conservative approach. In every case, the complexity of the disease calls for special consideration and decisions should always be made on a multidisciplinary team basis.

PATIENT CONSENT

Written informed consent was obtained from the patient.

CONFLICT OF INTEREST

None

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None

REFERENCES

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CASE REPORT

Primary spinal melanoma

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ABSTRACT
Primary malignant melanoma of the spine is a rare neoplasm with scarce data supporting clinical and radiological diagnosis, treatment, and prognosis. Resection is the preferred treatment, while some investigators recommend postoperative chemotherapy, immunotherapy, and/or radiotherapy. Our goal was to present an exceptionally unusual example of primary malignant melanoma located in the lumbar spine.

KEYWORDS
Lumbar spine, Melanoma, CNS

ΠΕΡΙΛΗΨΗ
Το πρωτοπαθές κακόηθες μελάνωμα της σπονδυλικής στήλης είναι ένα εξαιρετικά σπάνιο νεόπλασμα με λίγα δεδομένα διαθέσιμα αναφορικά με την κλινική και ακτινολογική διάγνωση, τη θεραπεία και την πρόγνωση. Η χειρουργική εξαίρεση είναι η θεραπεία εκλογής, ενώ ορισμένοι ερευνητές συνιστούν μετεγχειρητική χημειοθεραπεία, ανοσοθεραπεία και/ή ακτινοβολία. Στόχος μας ήταν να παρουσιάσουμε μια εξαιρετικά σπάνια περίπτωση πρωτοπαθούς κακοήθους μελανώματος στην οσφυϊκή μοίρα της σπονδυλικής στήλης.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ
Σπονδυλική, μελάνωμα, κεντρικό νευρικό σύστημα.

INTRODUCTION

Primary melanoma of the central nervous system (CNS) is exceedingly rare, accounting for only 1% of all melanomas. The most frequent locations are the brain, followed by the cervical, thoracic, and lumbar spine. CNS melanomas have a better prognosis compared to cutaneous or metastatic melanomas, but due to the rarity of cases, definitive conclusions cannot be drawn. The only treatment available is surgical removal of the tumor [1-3]. We present herein a case of a 73-year-old male with primary malignant melanoma of the lumbar spine who underwent subtotal surgical resection.

CASE REPORT

A 73-year-old Caucasian male patient presented to the Neurosurgery Department of the University Hospital of Ioannina with progressive loss of motor function in both legs over the last 48 hours. This was accompanied by urinary retention and constipation. On neurological examination, both the left and right lower limbs had muscle power of 2/5 according to the Medical Research Council scale. Sensation and deep tendon reflexes were normal in both limbs. A lumbosacral MRI revealed an intradural lesion at the level of the cauda equina, with a vertical diameter of 19mm. Several smaller lesions with a similar appearance were observed below this lesion. A brain MRI revealed a lesion in the right cerebellar hemisphere, with recent hemorrhagic content but no perilesional edema. The patient was operated and a L2 laminectomy was performed. After opening the dura, we identified a mass and we noted the dark appearance of nearly all the nerve roots. Macroscopically and under the microscope, it appeared that melanotic tissue had infiltrated the cauda equina and extended to the conus medullaris [Figure 1].

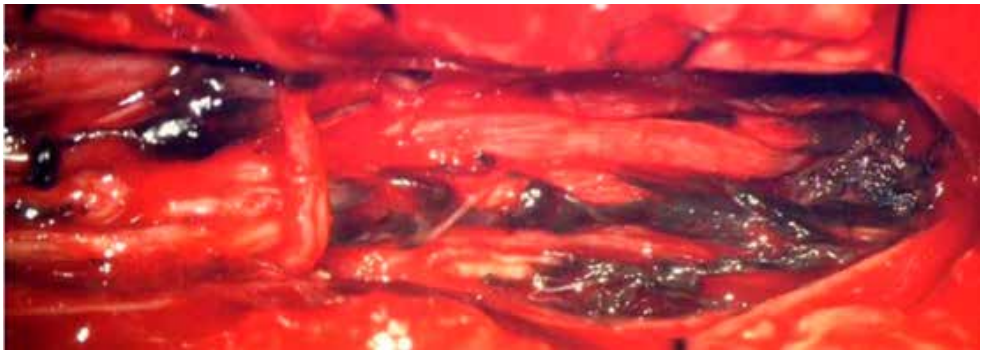

Figure 1. Intraoperative photo revealing the melanotic tissue.

After an intraoperative pathology consultation, which confirmed a diagnosis of melanocytic tumor, and due to the diffuse infiltration without clear borders, we performed subtotal resection of these lesions.

Histopathological examination of tumor fragments on permanent tissue sections revealed a cellular neoplasm composed of large epitheliod cells arranged in sheets or fascicles or loose nests. Tumor cells displayed pleomorphic large nuclei, prominent nucleoli and numerous mitotic figures. Variable amounts of black to brown pigment were observed in the cytoplasm of neoplastic cells as well as in the extracellular stroma. Areas of coagulative necrosis were also demonstrated [Figure 2]. By immunohistochemistry, the tumor cells were strongly positive for melanocytic markers such as S100, SOX10, Melan A and HMB45 [Figure 3]. The findings were consistent with a malignant neoplasm with melanocytic differentiation and melanoma was considered as the most probable scenario in the diagnostic approach.

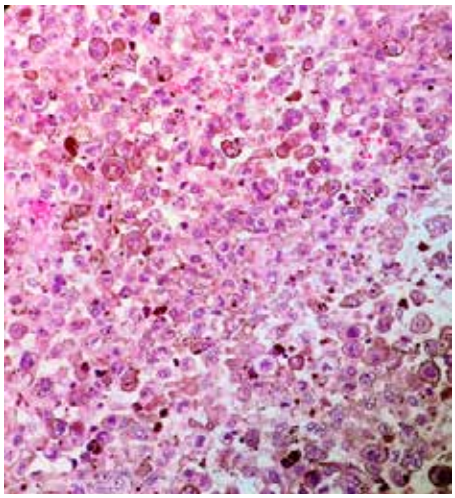

Figure 2. Histology revealed large epithelioid, pleomorphic and pigmented tumor cells arranged in sheets (Hematoxylin-eosin stain, original magnification X 200).

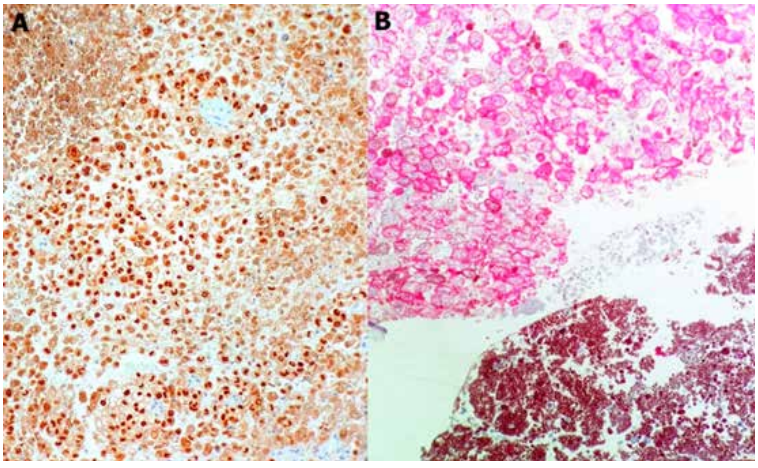

Figure 3. A. SOX10 and HMB45 (B) immunohistochemical positivity highlights the melanocytic differentiation of the tumor cells (Immunohistochemical stains, original magnification X 100 & X200, respectively).

The patient was examined by dermatologists and ophthalmologists, who found no melanotic lesions on the skin or eyes. According to the Hayward classification, this was a primary melanoma. The patient remained bedridden, and his caregivers did not consent to further interventions. He passed away within two months.

DISCUSSION

Most CNS melanomas are metastatic (approximately 90%), making melanoma the third most common source of CNS metastasis, following breast and lung cancers [1,4]. Only 1% of all melanomas affect the CNS, and primary spinal cord melanomas are even rarer. This explains why cases such as this one are infrequently reported. MRI is the diagnostic tool of choice for spinal cord tumors. The differential diagnosis includes ependymoma, astrocytoma, melanocytoma, and melanotic schwannoma [5]. The vast majority of CNS melanomas result from metastasis, and primary spinal cord melanoma is an extremely rare condition, with fewer than 70 cases reported in the literature. Primary melanomas of the spinal column are more commonly located in the cervical and thoracic regions [6].

Whenever possible, complete surgical excision should be performed. In cases where only a biopsy can be obtained, the absence of clear borders indicates a more diffuse and infiltrative lesion, as observed in MRI findings. Radiological features can vary due to the paramagnetic susceptibility effect of melanin and intratumoral hemorrhage, making pathological examination essential for diagnosis. In most cases, radiotherapy and chemotherapy are recommended, but the prognosis is poor due to the high rate of dissemination by the time of diagnosis [7].

PATIENT CONSENT

Written informed consent was obtained from the patient.

CONFLICT OF INTEREST

None

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None

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