Aggressive Angiomyxoma.
A case series of eight years of experience

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BACKGROUND: *Aggressive angiomyxoma is a type of mesenchymal tumor occurring predominantly in the pelvic and perineal region. The aim of our study was to reveal our experience with gonadotropin-releasing hormone (GnRH) treatment in patients with angiomyxoma and provide a comprehensive review of management.*
PATIENTS AND METHODS: *This study is a case-series including seven female patients diagnosed with aggressive angiomyxoma from a single institution, between 2012 and 2020. Follow-up after surgery was ranged between 2-45 months with an average of 17.6 months. Resection was performed in all patients without any complications, and five had received GnRH analogue (Goserelin acetate) therapy after surgery. Immunohistochemistry analyses showed positivity for smooth muscle actin and desmin in all cases, while both estrogen receptor (ER) and progesterone receptor (PR) positivity were identified in 6 patients. None of the seven patients had recurrence during follow up period.*
CONCLUSION: *The mean treatment of aggressive angiomyxoma is surgery, and the use of GnHR analogues in cases with positive ER and PR may be effective in preventing recurrence.*

KEY WORDS: Aggressive Angiomyxoma, Gonadotropin-Releasing Hormone, Soft Tissue Neoplasm

Introduction

Aggressive angiomyxoma (AA) is an uncommon, slow growing with local recurrence and rare metastasis mesenchymal tumor which has been well established after its initial description by Steeper and Rosai in 1983 [1]. The tumor exhibits variably myxoid, mesenchymal characteristics and occurs predominantly in the pelvic and perineal region with a reported female to male ratio of 6:1. Patients are often admitted because of a non-tender palpable mass in the vulva, or the tumor tissue is incidentally identified via imaging modalities [2,3].

Total excision with wide tumor-free margins is the curative treatment, while gonadotropin-releasing hormone (GnRH) analogues, aromatase inhibitors and estrogen / progesterone receptor blockers are useful neoadjuvant strategies to reduce recurrence rates and/or facilitate resection [4,5]. GnRH analogues have been reported a potentially curative medical therapy, as an alternative or additional option to surgery. On the other hand, GnRH analogue treatment is demonstrated to result in significant reduction of neoplastic tissue and even complete regression in the case of small growths [6]. Indeed, the presence of estrogen receptor (ER) and progesterone receptor (PR) positivity suggest that hormones have considerable influence in stimulating the growth of these tumors; thus, supporting the rationale for the use of GnRH agonists in the treatment of AA.
The purpose of this study was to reveal our experience with the use of a hormonal therapy (GnRH; goserelin acetate) in conjunct with surgical excision for the treatment of AA in seven patients. We also provide a review of current literature pertaining to hormone therapies in AA.

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Case Reports

This case includes data from seven patients diagnosed with aggressive angiomyxoma who had received treatment at a single institution, from January 2012 to December 2020. Ethical approval for this study was received from the Institutional Review Board of Tepecik Training and Research Hospital, Turkey.

All of the cases underwent diagnostic procedures and received treatment in our center. Age, size and location of tumor, gravidity, parity and immunohistochemical characteristics (Smooth muscle actin, Vimentin, Desmin, ER, PR, Ki67, CD34, S-100) were recorded. Surgical resection was the primary treatment of choice in all cases and pathological examination of specimens were performed. Patients 2, 3, 5, 6 and 7 also received GnRH analogue therapy via subcutaneous administration of goserelin acetate (Zoladex® 3.6 mg goserelin, AstraZeneca) into the anterior abdominal wall, once every 28 days.

The seven patients in the study were aged 29 to 47 years, mean age was 37.4 years. The follow-up time after surgery ranged from 2 to 45 months with an average of 17.6 months. The mean follow-up time was 16 months (range 2-43 months) (Table I). Of the patients studied, none presented with any definite contraindications to surgery; thus, resection surgery was scheduled after the confirmation of diagnosis in all cases. All surgical specimens demonstrated spindle cells scattered in a myxoid and collagen background with an abundance of vessels in microscopic analyses. Immunohistochemistry analyses showed positivity for smooth muscle actin and desmin in all cases, while both estrogen receptor (ER) and progesterone receptor (PR) positivity were identified in 6 patients (Table II).

Apart from patients 5 and 7, all resections were performed in a routine manner and were uneventful. In case 5, an 8-cm-sized residue in the vulvar area remained after the procedure due to anatomically challenging localization. The patient received 7 months of goserelin administration and underwent secondary surgery–a debulking procedure including total mass excision, urethral dissection, bladder dissection and primary bladder repair. The second-line goserelin administration therapy has lasted for 12 months as of writing and no growth or recurrence has been observed. There were no mortalities or complications in relation with the tumors or the surgeries. None of the patients had metastasis development. Five subjects (patients 2, 3, 5, 6 and 7) who had ER and PR positivity were treated with goserelin acetate, while patient number 4, also positive for ER and PR, refused hormone therapy (Table I). None of the patients included in this study had recurrence during follow-up.

Discussion

Aggressive angiomyxoma occurs predominantly in premenopausal females, suggesting a role for estrogen in its growth. This concept is perhaps most strongly support-

Table I - *Clinical characteristics of the patients*

Patient no.	Age (years)	Gravida, Para	Location	Size	GnHR (duration of medication)	Follow-up (months)
AM 1	30	G2P2	Right side of the vagina	8 cm	–	2
AM 2	29	G1P1	Left labium majus	11 cm	+ (6 months)	6
AM 3	29	G0P0	Left labium majus	7.5 cm	+ (6 months)	19
AM 4	44	G2P2	Posterior fourchette	3 cm	–	45
AM 5	37	G2P2	Left labium majus	9 + 8 cm (Residue)	+ (12 months)	24
AM 6	47	G8P8	Left labium minus	10 cm	+ (12 months)	13
AM 7	46	G2P2	Left labium majus	20 cm	+ (3 months)	3

Age; at initial presentation, GnHR; gonadotropin-releasing hormone (goselerine).

Table II - *Immunohistochemical features of tumors*

Patient no.	SMA	Vimentin	Desmin	ER	PR	Ki67	CD34	S-100
AM 1	+		+				-	-
AM 2	+	+	++	+	+	+	+	
AM 3	+	+++	++	+++	+++	+	+	
AM 4	+	+	+	+	+	+	+	
AM 5	+		+	+	+		-	-
AM 6	+		+	+	+		+	
AM 7	+		+	+	+		+	-

SMA; Smooth muscle actin, ER; estrogen receptor, PR; progesterone receptor

ed by a case report that demonstrated rapid growth of an aggressive angiomyxoma during pregnancy -which is a state of increased estrogen and progesterone production [7]. Although there are numerous reports of cases in the scrotum, spermatic cord and the pelvic region of elderly males, AA is exceedingly rare among males [8,9] . Such tumors may be misdiagnosed as Bartholin's cyst, abscess or hernia especially when patients complain of pain in the perineum, labia or pelvis. Therefore, microscopic analyses, immunohistochemical results and imaging findings have become crucial in diagnosis. The infiltrative nature of these tumors can be observed in the periphery where the myxoid tissue is seen extending into fat, skeletal muscle or other structures. Histological differentiation may be difficult from myxoid neurofibromas, myxoma, myxoid liposarcomas or fibrosarcomas, sarcoma botyroides, vaginal botyroid pseudosarcoma, myxoid leiomyosarcoma and myxoid type malignant fibrous histiocytoma. In the present study, postoperative pathology revealed that all specimens were consistent with angiomyxoma appearance. Immunohistochemistry staining for vimentin, desmin, smooth muscle actin, CD34, ER and PR are also supportive for angiomyxoma diagnosis in clinically compatible cases [10-13]. In the current patient group, desmin and smooth muscle actin were positive in all of the cases, while positivity for ER (6/7), PR (6/7) and CD34 (5/7) were also frequent. Additionally, S-100 positivity was not observed in any patient.

Since surgical resection is the primary mode of treatment, appropriate pretreatment imaging is critical to provide the surgeon with relevant information about the true extent of the tumor, especially in relation to infiltration characteristics and lesion size which has been shown to vary greatly from 1 to 60 cm [14]. In this report, we observed a lesion with almost 20 cm diameter in the greatest dimension. AA is considered as a non-metastasizing tumor even though some cases of distant metastases have been documented in the literature, particularly in the lungs [15,16]. The fact that such cases are exceedingly rare translates into overwhelmingly positive results with surgical resection; however, there may be a need for supportive medical treatment in select cases, especially those wherein resection is incomplete. Considering ER and PR positivity in most cases, the treatment of AA with GnRH agonists (which induce a hypoestrogenic state) has emerged as an option, but response can be variable [17].

The use of GnRH analogues, both agonists and antagonists, may also have protective effects on the ovaries, as demonstrated in animal studies [18,19]. This may be an advantageous effect since most patients diagnosed with angiomyxoma are of childbearing age. In this report, the age interval was between 29 to 47 years and mean age was 37.4 years.

Previous authors have described that multiple excisions with wide tumor-free margins may be necessary to obtain a cure [4]. In a remarkable study, Fine et al. reported the case of a 27-year-old woman with wide recurrent aggressive angiomyxoma. The patient did not accept radical surgical resection. Subsequently the patient received a GnRH agonist for three months. Repeated CT imaging showed gradual but significant reduction in tumor size, and ultimately the tumor was deemed to have complete regression. However, follow-up information was not provided about whether the tumor had recurred after termination of therapy [5]. In the present study, we report that no patients had recurrence during their respective follow-up periods. More specifically, the four GnRH recipients, with follow-up durations ranging from 3 to 12 months, were not found to have recurrence. Comparisons in this regard were not possible due to the limited number of patients included in the study and it is evident that future studies should aim to conduct long term assessments, possibly in multicenter trials due to the rarity of AA.

Conclusion

This is one of the few studies that reports short to mid-term follow-up analysis of patients who had received goserelin after surgical excision. The data reported in this study may be significant for physicians, notwithstanding the small number of cases, and may be utilized as a guide for patient management and treatment expectations. Although results seem to be encouraging, it is evident that future studies are necessary to elucidate the value of post-surgical treatment with GnRH agonists in patients with AA.

Riassunto

Premessa: l'angiomixoma aggressivo è un tipo di tumore mesenchimale che si verifica prevalentemente nella regione pelvica e perineale. Lo scopo del nostro studio era di rivelare la nostra esperienza con il trattamento con ormone di rilascio delle gonadotropine (GnRH) in pazienti con angiomixoma e fornire una revisione completa della gestione.

Pazienti e Metodi: questo studio è una serie di casi che include sette pazienti di sesso femminile con diagnosi di angiomixoma aggressivo da un singolo istituto, tra il 2012 e il 2020. Il follow-up dopo l'intervento chirurgico è stato compreso tra 2 e 45 mesi con una media di 17,6 mesi. La resezione è stata eseguita in tutti i pazienti senza complicazioni e cinque avevano ricevuto una terapia con analogo del GnRH (Goserelin acetato) dopo l'intervento chirurgico. Le analisi immunoistochimiche hanno mostrato positività per l'actina e la desmina della muscolatura liscia in tutti i casi, mentre in 6 pazienti è stata identificata la positività sia del recettore degli estrogeni (ER) che del recettore del progesterone (PR).

Nessuno dei sette pazienti ha avuto recidiva durante il periodo di follow-up.
CONCLUSIONE: il trattamento medio dell'angiomixoma aggressivo è la chirurgia e l'uso di analoghi del GnHR nei casi con ER e PR positivi può essere efficace nel prevenire le recidive.

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