Abstract. Mazabraud's syndrome (MS) is a rare disease that is a combination of fibrous dysplasia and intramuscular myxomas. MS is a benign lesion and there is little data on the disease due to its low incidence. In the present study, the case of a 38-year-old patient who presented with a soft-tissue mass involving the masseter and swelling at the mandibular body and mandibular ramus is reported. Since the mandible is an important aesthetic and functional organ in the oral and maxillofacial region, surgery was primarily aimed at resecting the tumor, with good safety margins, and reconstructing the resultant defect. The lesions were pathologically diagnosed as MS. The unique features of this case included the painless and monostotic fibrous dysplasia, the solitary intramuscular myxomas involving the jaw and the male gender of the patient. MS usually occurs in the lower extremities, with an unusual predilection for the right limb; however, it rarely occurs in the head and neck region. A retrospective analysis of the clinical features and management of MS was also performed in the present study, together with a literature review. From the literature, it was concluded that the incidence of MS is ~2.3-fold greater in female patients than in male patients, and that the age of onset of MS ranges between 17 and 82 years, with an average age of 46.25 years.

Introduction

Mazabraud's syndrome (MS) is a rare benign syndrome that is reported to be associated with single or multiple intramuscular myxomas and fibrous dysplasia occurring in a single or multiple bones. Intramuscular myxoma in itself is a relatively uncommon benign mesenchymal tumor (1), while fibrous dysplasias are more frequent benign lesions (2). To the best of our knowledge, 92 cases of MS have been reported in the medical literature thus far. However, only 9 cases have reported the combination of a solitary myxoma and monostotic fibrous dysplasia (3-10). MS involving the mandible and the adjacent soft tissue of the bone lesions was reported by Logel (11). However, MS of the masseter and the mandible are rarely reported compared with other regions. The aim of the current study was to present a novel case of solitary myxoma and monostotic fibrous dysplasia involving the jaw and the masseter. Additionally, an overview of the 92 reported cases of MS is also presented.

Case report

On February 8th, 2014, a 38-year-old male patient presented to the Shanghai Ninth People's Hospital (Shanghai, China) with a history of a slowly growing painless swelling in the left mandibular area that had been present for 23 years. A definitive diagnosis had not been reached upon examination at a local hospital (Zhengzhou, China) in 2011. The patient had undergone a pathological biopsy prior to the current examination and was diagnosed with ossifying fibroma in another hospital (Zhongshan Hospital, Zhengzhou, China). The current physical examination identified two masses, one on the left mandible and one on the left musculus buccinator. The left mandibular lump measured ~5 cm in diameter, was hard in nature and protruded from the surface with ill-defined margins. There was no visible disease activity and no palpable tenderness. The soft-tissue swelling located in the musculus buccinator near the left mandibular measured ~3 cm in diameter; the lesion exhibited no visible ulceration and no palpable tenderness (Fig. 1). Conventional panoramic radiography demonstrated a hazy shadow of low but uneven density, often with ill-defined margins in the mandible. The patient did not present with any bony deformities or café-au-lait spots. Computed tomography (CT) and three-dimensional CT reconstruction in the oral and maxillofacial regions showed that the mass exhibited a localized ‘ground-glass’ pattern on the left mandibular body and mandibular ramus, and an uneven high-density shadow.
was identified (Fig. 2). The buccal bone cortex of the mass was discontinuous. Adjacent soft tissue was markedly thickened, with uniform density.

A pre-operative diagnosis of single intramuscular myxoma and a benign bone lesion was determined and histopathologically confirmed following resection of the lesions. The left mandible lesions and outermost region of the bony plates of the ramus were completely resected, while conserving the condyle. Next, a free fibular osteocutaneous flap with skin island reconstruction was performed. During the surgery, a soft-tissue mass of 3.5x2.5x1.0 cm was resected. Histological examination of the left mandibular lesions showed immature woven bone trabeculae devoid of osteoblastic lining laid in proliferative fibrous connective tissue, and the lesions were characterized by some mucous degeneration and were hypercellular enough to be characterized as fibrous dysplasia. The histopathological examination of the buccal mass revealed a tumor extending into the striated muscle, formed from hypocellular tissue with bland stellate cells and spindle-shaped cells within a polysaccharide abundant myxoid matrix. A histopathological diagnosis of intramuscular myxoma was formed. Immunohistochemical analysis showed positive staining for vimentin and cluster of differentiation (CD)99, and negative staining for desmin, smooth muscle actin, B-cell lymphoma-2, S-100 protein and CD34. The intramuscular myxoma with adjacent fibrous dysplasia was diagnosed as MS (Fig. 3). Follow-up examinations were planned every 3-6 months for 3 years. Three and six months after surgery, MRI follow-up examinations revealed that the
patient exhibited no clear evidence of recurrence of myxoma and fibrous dysplasia. However, the patient has subsequently been lost to follow-up.

This study was approved by the Shanghai Ninth People’s Hospital Institutional Review Board and the patient provided written informed consent.

Discussion

MS was first described in the German literature by Henschen in 1926 (12), and Mazabraud et al presented a pattern of association between fibrous dysplasia and soft-tissue myxomas in 1967 (13). Only a limited number of cases appear in the literature. Not including the present case, ~92 cases of what has come to be termed as ‘Mazabraud’s syndrome’ have been described in the literature to date (Table I) (3,5-75).

MS is an uncommon type of benign tumor that mainly occurs in the lower limbs (14). In the most extensive review of MS to date in the literature, the present study found 9 cases of the unusual association of monostotic fibrous dysplasia combined with a rare solitary myxoma. A mandibular origin accounted for ~10 cases.

Six of these cases were excluded from the study because we were not get detailed information (3,6,9,15-17), therefore, including the present case, a total of 87 cases were reviewed. Table I reveals that the majority of affected patients were female (61 cases). While only 26 cases were male, indicating an ~2.3-fold greater incidence in females than in males. The most common onset of fibrous dysplasia is polyostotic, present in 70 cases (80.46%). In 17 cases, fibrous dysplasia was monostotic (19.54%). However, these myxomas were solitary in 40 cases (45.98%). Monostotic fibrous dysplasia and solitary myxoma, when associated, is a rare condition. Only a few cases were mentioned in the literature. Another common finding of MS that was recorded in the literature was its localization in the lower extremities, which occurred in 82.71% of cases (67 in the lower extremities, 35 in the upper extremities, 19 in all four extremities and in 11 in the head and neck; in 6 cases, detailed information was not recorded). These tumors were bilateral in 30 cases and unilateral in 51 cases. This finding is in agreement with other studies, which confirm that the majority patients with MS have multiple intramuscular myxomas and polyostotic fibrous dysplasia that tend to be located in the lower extremities, with a particular predilection for the lower right limb (18). The age of onset of MS in the 87 patients studied ranged between 17 and 82 years, with an average age of 46.25 years. MS was most commonly diagnosed in the middle-aged population.

The case reported in the present study differs from the majority of the previously reported cases due to its rare localization in the head and neck, specifically the mandible, in addition to the unusual association of monostotic fibrous dysplasia and solitary myxoma. As the mandible is an important aesthetic and functional organ in the oral and maxillofacial region, an accurate pre-operative estimation of mandibular invasion remains challenging.

Another unusual aspect of the present study was the complex appearance of histopathological findings of the mucous degeneration of fibrous dysplasia. It is rare to find the mucous transformation of fibrous dysplasia that was observed in this case in patients with MS. Although uncommon, malignant transformation of fibrous dysplasia can also occur in patients with MS (76).

Intramuscular myxomas are rare benign tumors of the musculoskeletal system that were first recognized as a definite clinicopathologic entity by Enzinger in 1965. The study presented a brief compilation of 34 examples of intramuscular myxoma and demonstrated the benign clinical course of the tumor, as relatively few of the cases exhibited a tendency to metastasize (77). While intramuscular myxoma is rare, fibrous dysplasia is not. Fibrous dysplasia is a congenital disease characterized by a condition affecting one, several or numerous bones, leading to osteolytic lesions, deformities and fractures (78). Intramuscular myxoma is usually a solitary lesion, and exhibits an association with multiple fibrous dysplasia (19). Occasionally, MS is associated with McCune-Albright syndrome (MAS) (20). MAS is a rare syndrome with the three combined characteristics of polyostotic fibrous dysplasia, endocrine dysfunction and café-au-lait spots (79).
Table I. Reported cases of Mazabraud's syndrome.

| First author/s, year (ref.)                          | Gender | Age, years | Fibrous dysplasia | Myxoma | Lesion localization |
|------------------------------------------------------|--------|------------|-------------------|--------|---------------------|
| Henschen, 1926 (12)                                  | Female | 66         | Monostotic        | Multiple | R-L                 |
| Krogius, 1929 (23)                                   | Female | 26         | Polyostotic       | Multiple | B-U/B-L             |
| Uehlinger, 1940 (24)                                 | Male   | 67         | Polyostotic       | Single   | R-L                 |
| Braunchwarth, 1953 (5)                               | Female | 55         | Polyostotic       | Single   | R-L                 |
| Mazabraud and Girard, 1957 (25)                      | Male   | 54         | Polyostotic       | Multiple | R-U'R-L             |
| Heinemann and Woerth, 1958 (26)                     | Female | 82         | Polyostotic       | Multiple |                     |
| Laporte, 1961 (27)                                   | Female | 24         | Polyostotic       | Single   |                     |
| Lick, 1962 (28)                                      | Male   | 59         | Polyostotic       | Multiple |                     |
| Mazabraud, 1967 (13)                                 | Female |            | Polyostotic       | Multiple |                     |
| Roze, 1967 (29)                                      | Female | 38         | Polyostotic       | Multiple | B-U/B-L             |
| Semat, 1969 (30)                                     | Male   | 47         | Polyostotic       | Single   | B-U/B-L             |
| Wirth et al, 1971 (31)                               | Male   | 17         | Polyostotic       | Multiple | B-U/B-L             |
| Male                                                 | 33         | Polyostotic       | Multiple | B-U/B-L'H&N         |
| Lejeune, 1972 (32)                                   | Male   | 41         | Polyostotic       | Multiple | B-U/B-L             |
| Ireland, 1973 (33)                                   | Female | 49         | Monostotic        | Multiple | B-U/B-L             |
| Female                                               | 59         | Polyostotic       | Multiple | R-L                 |
| Female                                               | 28         | Polyostotic       | Multiple | R-L                 |
| Logel, 1976 (11)                                     | Female | 41         | Polyostotic       | Multiple | B-U/B-L'H&N         |
| Berkhoff, 1981 (6)                                   | Male   | 50         | Polyostotic       | Single   |                     |
| Sedmak, 1983 (34)                                    | Male   | 50         | Polyostotic       | Single   | L-L                 |
| Lever and Pettingale, 1983 (35)                      | Female | 50         | Polyostotic       | Single   | B-U/B-L             |
| Segev and Reiner, 1985 (3)                           | Female | 46         | Polyostotic       | Single   | R-L                 |
| Witkin, 1986 (36)                                    | Male   | 40         | Polyostotic       | Single   | B-L                 |
| Blasier, 1986 (37)                                   | Female | 57         | Polyostotic       | Multiple | L-U/L-L             |
| Biagini, 1987 (38)                                   | Female | 42         | Polyostotic       | Multiple | B-U/B-L             |
| Glass-Royal, 1989 (39)                               | Male   | 42         | Polyostotic       | Single   | B-U'H&N             |
| Sundaram, 1989 (40)                                  | Female | 31         | Polyostotic       | Multiple | R-L                 |
| Gianoutsos, 1990 (41)                                | Male   | 53         | Monostotic        | Multiple | R-L                 |
| Prayson, 1992 (42)                                   | Female | 36         | Polyostotic       | Single   | R-U                 |
| Gober and Nicholas, 1993 (43)                        | Female | 37         | Monostotic        | Multiple | L-L                 |
| Aoki, 1995 (44)                                      | Female | 67         | Polyostotic       | Multiple | B-U/B-L             |
| Female                                               | 46         | Polyostotic       | Single   | R-L                 |
| Fujii, 1996 (45)                                     | Female | 47         | Monostotic        | Single   | B-U/B-L             |
| Limouzy, 1996 (7)                                    | Male   | 45         | Monostotic        | Single   | R-L                 |
| Court-Payen, 1997 (46)                               | Female | 50         | Polyostotic       | Multiple | R-U'H&N             |
| Szendroi, 1998 (22)                                  | Female | 52         | Polyostotic       | Multiple | B-L                 |
| Female                                               | 34         | Polyostotic       | Multiple | B-L                 |
| Female                                               | 54         | Polyostotic       | Single   | L-L                 |
| Cabral, 1998 (47)                                    | Male   | 44         | Polyostotic       | Multiple | R-L'H&N             |
| Lopez-Ben, 1999 (21)                                 | Female | 40         | Polyostotic       | Multiple | B-U/B-L'H&N         |
| Thomacot, 1999 (48)                                  | Female | 36         | Polyostotic       | Single   | L-L                 |
| Walker, 1999 (49)                                    | Male   | 36         | Polyostotic       | Single   | R-L                 |
| Kransdorf and Murphey, 1999 (50)                     | Female | 67         | Monostotic        | Multiple | R-L                 |
| Okamoto, 2000 (51)                                   | Female | 53         | Polyostotic       | Multiple |                     |
| Female                                               | 34         | Polyostotic       | Multiple | B-U/B-L             |
| Female                                               | 38         | Polyostotic       | Single   | L-L                 |
| Struk, 2000 (8)                                      | Female | 53         | Monostotic        | Single   | R-L                 |
| Faivre, 2001 (52)                                    | Female | 35         | Polyostotic       | Multiple | B-U/B-L             |
| Male                                                 | 42         | Polyostotic       | Multiple | L-U'R-L             |
| Delabrousse, 2001 (53)                               | Female | 40         | Monostotic        | Multiple | R-L                 |
| Pollandt, 2002 (54)                                  | Female | 42         | Polyostotic       | Multiple | B-L                 |
The clinical presentation of MS is similar to that of fibrous dysplasia and intramuscular myxoma. Myxoma may be diagnosed in adolescents or young adults with symptoms, but fibrous dysplasia is incidentally found on imaging studies. In a series of 66 patients, Zoccali et al (14) reported that the myxoma develops 12 years prior to the fibrous dysplasia diagnosis. Intramuscular myxoma is a rare, benign tumor of the musculoskeletal system, with a low incidence. The tumor may occur in isolation or in association with fibrous dysplasia or McCune-Albright syndrome (21). Pain and facial palsy are uncommon. The tumor

Table I. Continued.

| First author/s, year (ref.) | Gender | Age, years | Fibrous dysplasia | Myxoma | Lesion localization |
|----------------------------|--------|------------|-------------------|--------|--------------------|
| Iwasko, 2002 (55)          | Female | 39         | Polyostotic       | Multiple | L-L                |
| Fang, 2003 (57)            | Male   | 33         | Polyostotic       | Single  | R-L                |
| Jhala, 2003 (58)           | Female | 44         | Polyostotic       | Multiple | R-U                |
| Tsurouridis, 2002 (56)     | Female | 28         | Polyostotic       | Single  | B-U/B-L/H&N        |
| Fang, 2003 (57)            | Male   | 33         | Polyostotic       | Single  | R-L                |
| Jhala, 2003 (58)           | Female | 44         | Polyostotic       | Multiple | R-U                |
| Kabukcuoglu, 2004 (19)     | Female | 52         | Polyostotic       | Single  | L-L                |
| Nguyen and Ram, 2005 (59)  | Male   | 48         | Polyostotic       | Multiple | R-U                |
| Endo, 2007 (75)            | Female | 64         | Monostotic        | Single  | R-L                |
| Miyake, 2006 (9)           | Female | 52         | Polyostotic       | Multiple | L-L                |
| Martin, 2007 (60)          | Female | 52         | Polyostotic       | Single  | L-U                |
| McLaughlin, 2007 (61)      | Female | 53         | Polyostotic       | Single  | L-U                |
| Singurkar, 2007 (62)       | Male   | 42         | Polyostotic       | Multiple | H&N                |
| Calisir, 2007 (63)         | Female | 65         | Monostotic        | Multiple | L-L                |
| MacFarlane, 2007 (64)      | Male   | 45         | Polyostotic       | Multiple | B-U/B-L            |
| Schepers, 2008 (65)        | Male   | 35         | Polyostotic       | Single  | L-U                |
| Santos, 2008 (66)          | Male   | 48         | Polyostotic       | Single  | H&N                |
| Zhao, 2008 (10)            | Female | 60         | Monostotic        | Single  | R-L                |
| Beele, 2008 (15)           | Female | 40         | Polyostotic       | Single  | L-L                |
| Tagliafico, 2009 (67)      | Female | 63         | Polyostotic       | Single  | R-U                |
| Crawford, 2009 (12)        | Male   | 63         | Polyostotic       | Single  | R-U                |
| Tang, 2009 (16)            | Female | 32         | Polyostotic       | Single  | R-L                |
| Arishima, 2010 (3)         | Female | 71         | Monostotic        | Single  | L-L                |
| Case, 2010 (68)            | Female | 69         | Polyostotic       | Single  | L-U                |
| Ijima, 2010 (69)           | Female | 51         | Polyostotic       | Single  | B-L                |
| Kitagawa, 2011 (20)        | Female | 49         | Polyostotic       | Multiple | B-U                |
| van der Wal, 2011 (70)     | Female | 49         | Polyostotic       | Single  | L-L                |
| Yang, 2011 (17)            | Female | 56         | Polyostotic       | Multiple | B-L                |
| Gaumétou, 2012 (71)        | Male   | 40         | Polyostotic       | Multiple | L-U                |
| Schimmöller, 2012 (72)     | Female | 25         | Polyostotic       | Multiple | B-U/B-L            |
| John, 2013 (73)            | Female | 40         | Monostotic        | Multiple | L-U                |
| Munksgaard, 2013 (18)      | Female | 54         | Polyostotic       | Multiple | B-L                |
| Tsourdi, 2013 (74)         | Female | 45         | Polyostotic       | Single  | B-L                |
| Present study              | Male   | 38         | Monostotic        | Single  | H&N                |

R-L, right lower limbs; B-U/B-L, bilateral upper limbs/bilateral lower limbs; L-L, left lower limbs; L-U, left upper limbs; R-U, right upper limbs; H&N, head and neck.
can occur at any location and tends to involve the large muscles of the thighs, followed by the buttocks, arms, and chest wall and shoulders. The majority of intramuscular myxomas are two or more, painless, palpable masses that are firm, slightly movable and discrete. Moreover, the myxomas are most typically located in the are of the bone lesions (21). Fibrous dysplasia of the bone is a disease that is characterized by bone deformities, pain and pathological fractures. Patients can, however, be asymptomatic. Fibrous dysplasia can involve one bone (monostatic) or several bones (polyostotic) (80). There are few conditions which present as a solitary intramuscular mass in association with monostotic fibrous dysplasia. MS occurs at a younger age, may be associated with additional symptoms (café-au-lait spots and endocrine dysfunction) (81) and is often operable. The patient may also experience a long survival time with the tumor.

Imaging is useful in the verification of the lesions, particularly for the diagnosis of fibrous dysplasia. Ultrasound examination is safe for the patient and is necessary for the diagnosis of intramuscular myxoma. The typical ultrasound features of MS are considered to be well-defined, hypoechoic masses that are formed from numerous small, fluid-filled spaces that join to form a macrocystic pattern (22). CT scans, particularly coronal view scans, are useful in determining the size and quantity of fibrous dysplasia lesions, as well as verifying any bony involvement.

The optimal treatment for MS is surgical excision. Although MS is a benign tumor, it has a tendency to recur, with an accompanying risk of malignant transformation if incompletely excised and commonly requiring 'second-look' surgery (82). The rate of recurrence depends on the surgical approach. The surgical treatment of fibrous dysplasia is mostly indicated where there are progressive deformities, or a risk of fracture or pathological fracture. When the lesions occur in the jaw, the main aim of surgery is tumor resection, with good safety margins, and the reconstruction of the resultant defect, as this is important for the aesthetics and function of the oral and maxillofacial region (83). In the present case, free fibular osteocutaneous flap reconstruction was performed. For myxoma, a total excision is necessary and curative (84). When excluding differentials, such as primary malignancy or metastatic tumors, a full histopathological investigation should be performed for the lesions.

The precise etiology of fibrous dysplasia in association with myxoma remains unclear. The G protein/cAMP/adenylate cyclase signaling pathway that is central to the tissues involved in MAS led to the conclusion that regulatory Gsα protein (encoded by the GNAS gene) mutations were the underlying molecular etiology of MS (84). This theory is gradually becoming accepted.

In conclusion, clinicians should be aware of Mazabraud's syndrome in order to successfully manage patients with fibrous dysplasia in association with soft tissue myxomas and prevent misdiagnosis of this benign clinical entity as a malignant condition. In addition, differential diagnosis must be continued during clinical treatment when evaluating intramuscular lesions in the context of associated fibrous dysplasia.

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