Fibrous dysplasia

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Chapter 5

Prevalence and clinical features of Mazabraud's syndrome: a multicentre European survey

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ABSTRACT

Background: Mazabraud's syndrome is a rare disorder, characterized by the association of fibrous dysplasia (FD) with intramuscular myxomas. Data are scarce on the prevalence, clinical features, natural history and prognosis of this disorder. In this multicentre study of the European Musculo-Skeletal Oncology Society (EMSOS), we evaluate a series of patients from six European Centers.

Methods: All centers affiliated to the EMSOS were invited to include data on all patients with Mazabraud's syndrome who were seen in their centers between 1980 and 2015. Questions addressed included prevalence of Mazabraud's syndrome, type, severity and localization of FD lesions in relation to the myxomas, histopathology of myxomas and *GNAS*-mutation analysis when available.

Results: Thirty-two patients (22 female) from 6 centres were included in the study. The prevalence of Mazabraud's syndrome was 2.2% in the combined cohort of 1446 patients with FD and the syndrome was diagnosed a mean of 10.1 years after diagnosis of FD. The myxomas were predominantly localized in the upper leg. Excision was performed in 19 patients, recurrence occured in 6 (32%) and revision surgery was necessary in 5 (26%) after a median of 8.5 years (range 1.9–16.0). High cellularity of a myxoma was associated with recurrence ($p < 0.05$). A *GNAS*-mutation was identified in 5 of the 6 (83%) myxomas.

Conclusion: This study is the first to provide data on the prevalence of Mazabraud's syndrome. Although outcomes of surgical resection were good, a quarter of the patients required revision surgery despite free resection-margins. High cellularity of myxomas was identified as a risk factor for recurrence. *GNAS*-mutations were identified in 83%, emphasising the shared origin of FD and myxomas. Our data show that FD patients with disproportionate complaints, irrespective of type, extent or severity, should be investigated for the possible presence of myxomas. Finally, this study represents a fine example of how international collaboration provide unique opportunities for investigating extremely rare entities such as the Mazabraud's syndrome.

INTRODUCTION

Mazabraud's syndrome is an extremely rare syndrome, characterized by the association of skeletal fibrous dysplasia and intramuscular myxomas. The association of fibrous bony lesions with myxomas was first described by Henschen in 1926 and the syndrome was named after Mazabraud who made the link with fibrous dysplasia in 1967.[1,2] Fibrous dysplasia is a rare, genetic non-inheritable bone disorder caused by a postzygotic mutation of the *GNAS*-gene, which may affect a single (monostotic fibrous dysplasia) or multiple bones (polyostotic fibrous dysplasia), resulting in pain, deformities and pathologic fractures.[3] In the McCune-Albright syndrome, polyostotic fibrous dysplasia is associated with extraskeletal endocrine manifestations, such as precocious puberty, growth-hormone excess or hyperthyroidism and café-au-lait skin lesions. The *GNAS*-mutation that is responsible for the phenotype of fibrous dysplasia has also been identified in the soft tissue myxomas in Mazabraud's syndrome, suggesting a similar causality.[4-7] Mazabraud's syndrome is extremely rare in patients with fibrous dysplasia, with less than 100 cases reported to date in the literature.[8-10] Its prevalence has so far been estimated to be less than 1% in fibrous dysplasia. As often the case with very rare disease, little is known about several aspects of this syndrome such as pathophysiology, clinical characteristics, natural history and outcome of management. This formed the rationale for a number of European centres to join forces to participate in a in multicentre study, under the auspices of the European musculo-skeletal oncology society (EMSOS), to evaluate the prevalence and clinical characteristics of a relatively large combined series of patients with Mazabraud's syndrome. Here we studied the outcomes of surgical resection of the myxomas and possible risk factors for their recurrence, assessed the risk of malignant transformation of the fibrous dysplasia lesions as well as the myxomas, and evaluated the presence of *GNAS*-mutations in the myxomas.

PATIENTS AND METHODS

Study design

All affiliated centres of the EMSOS, were asked at the Society's 2016 Conference to collaborate in a study addressing the prevalence and clinical, radiological and pathological characteristics of Mazabraud's syndrome in their series of patients with FD followed up between 1980–2015 (Fig. 5.1). Six tertiary referral centres specialized in musculo-skeletal oncology answered the call, providing data on 32 patients with a confirmed diagnosis of Mazabraud's syndrome on the basis of clinical and radiographic

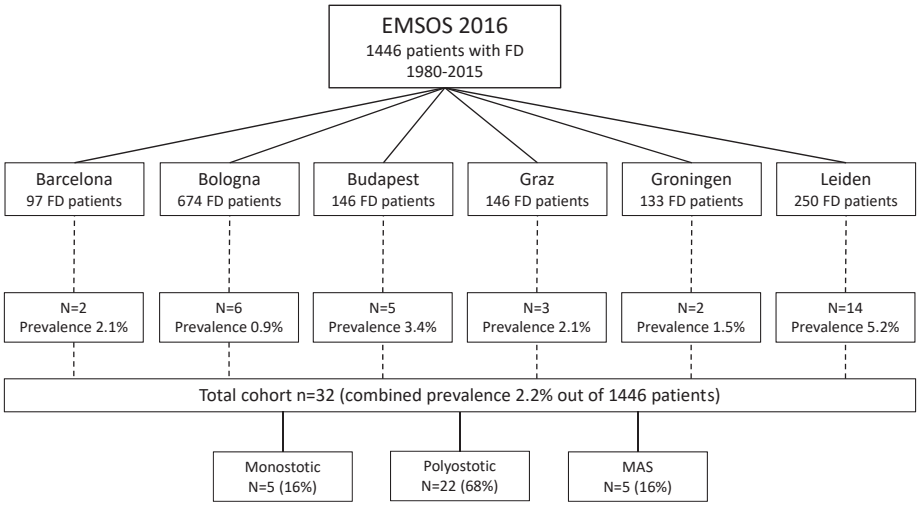


Fig. 5.1 Graph inclusion.

evidence for the association of fibrous dysplasia and myxomas, with additional histologic confirmation when required.

Data collection

The prevalence of Mazabraud's syndrome was evaluated in the combined cohort of 1446 patients with FD from the six centers. In patients identified as having Mazabraud syndrome, data was retrieved from hospital medical records on age, gender, type of fibrous dysplasia, age at diagnosis of fibrous dysplasia, localization of bony fibrous dysplasia lesions and possible malignant transformation of the fibrous dysplasia lesions or myxomas. Data were also retrieved on age at diagnosis of the myxomas, localization of myxomas, number of myxomas, size of the largest myxoma in individual patients.

Histopathology

Data on histopathology of myxomas were available in 17 patients. Myxomas were identified on the basis of the presence of typical bland spindle and stellate shaped cells with small nuclei in abundant extracellular myxoid stroma.[11] The level of cellularity of the myxomas retrieved from local pathology reports to be poorly cellular, intermediately cellular and highly cellular.[11]

Mutation analysis data

Data on *GNAS*-mutation analysis of the myxomas was extracted from the electronical patients records of 3 patients (Sanger sequencing) and was additionally performed in 3 patients using targeted Next Generation Sequencing according to a previously published protocol.[12]

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Results are presented as percentage, as mean ± standard deviation or as number and percentage. Differences in age at diagnosis of fibrous dysplasia and at diagnosis of the myxomas were analysed using a paired T-test. A Chi-Square test was used for differences between categorical data.

Source of funding

This study was supported by a research grant from the Bontius Foundation for research into fibrous dysplasia.

RESULTS

Epidemiology

Out of a total of 1446 FD patients from the combined cohort, 32 had an additional diagnosis of Mazabraud's syndrome, resulting in a combined prevalence of 2.2%. Individual prevalences of Mazabraud's syndrome were 5.6% (Leiden), 2.1% (Graz), 3.4% (Budapest), 1.5% (Groningen), 2.1% (Barcelona) and 1.0% (Bologna).

Clinical characteristics (Table 5.1 and 5.2)

The thirty-two patients identified as having the Mazabraud were predominantly female (22 female vs. 10 male). The majority of the patients (84%) had polyostotic FD (22 patients without extraskeletal manifestations and 5 with McCune-Albright syndrome) and only 5 patients had monostotic fibrous dysplasia. Fibrous dysplasia was diagnosed at a significantly younger age than Mazabraud's syndrome at a mean of respectively 37.3 ± 20.6 years vs. 47.4 ± 12 years ($p < 0.001$). The most prevalent localization for myxomas was the upper leg at locations within the quadriceps muscle (65.6%), the hip adductors (31.3%) and the gluteus muscles (21.9%) (Table 5.1). In all but one patient (97%) the myxomas were localized adjacent to the bony fibrous dysplasia lesions. One patient (nr. 32) had fibrous dysplasia of the humerus and

Table 5.1 Cohort characteristics

	(N = 32)
Gender (male/female)	10/22
Age at diagnosis in years	
Fibrous dysplasia	37.3 ± 20.6
Myxoma(s)	47.4 ± 12
Type of fibrous dysplasia	
Monostotic	5 (16%)
Polyostotic	22 (68%)
McCune-Albright syndrome	5 (16%)
Clinical manifestations at diagnosis	
Pain	19 (59%)
Painless swelling	5 (16%)
Neurological complaints	1 (3%)
No complaints	7 (22%)
Localization	
Quadriceps	59%
Hip adductors	31%
Gluteus muscles	22%
Latissimus dorsi	9%
Triceps	9%
Psoas major	9%
Gastrocnemicus	6%
Hamstrings	3%
Number of myxomas	
1	50%
2–5	25%
> 5	25%

Data are mean ± SD or number and percentage.

myxomas not only in the latissimus dorsi but also in the gluteus maximus, although he had no fibrous dysplasia lesions of the lower limb on conventional X-rays and MR-imaging. Fifty per cent of patients had more then one myxoma (range 2–20). Mean size of the largest myxoma per patient was 55.3 ± 26.4 mm. Clinical symptoms at diagnosis of the myxomas were pain (n = 19, 59%), painless swelling (n = 5, 16%) or neurological complaints (n = 1, 3%). Seven patients (22%) had no symptoms related to the myxomas, with these incidentally identified on routine radiological screening of the skeletal fibrous dysplasia lesions. Patients with symptomatic myxomas did not have more ($p = 0.890$) or larger ($p = 0.223$) myxomas than asymptomatic patients, and there were no significant differences in localisation of symptomatic compared

to asymptomatic myxomas. The clinical features and presentation of intramuscular myxomas are highlighted in a description of an illustrative case of Mazabraud's syndrome (Fig. 5.2).

Surgery (Table 5.3)

Nineteen patients (59%) underwent surgical removal of the myxomas(s), the majority (n = 17) because of complaints due to the myxomas(s) and two patients because of the possibility of the lesions being malignant. In all but one patient (case nr. 19), histopathogical evaluation of the myxomas revealed free resection margins. Despite free margins, recurrence of myxoma was reported in 6 cases (32%) after a median period of 8.5 years (range 1.9–16.0) and highly cellular lesions had a significantly higher recurrence rate of the resected myxomas ($p = 0.043$). Five patients (26%) had a second surgery performed, one of whom had a third removal. Only three complications of surgery were described: two patients (patient nr. 25 and 26) had delayed wound healing, which was adequately treated by debridement and one patient (patient nr. 25) developed temporary femoral nerve palsy after removal of the myxomas.

Histopathological reports of resected myxomas from 17 patients revealed variable cellularity between resected spcimens, with 9 myxomas categorized as highly cellular, one as intermediately cellular and 7 as poorly cellular. No malignant transformation was observed in any skeletal FD lesion or myxomas.

***GNAS*-mutation analysis (Table 5.4)**

Of the 6 patients in whom myxoma tissue was available, 5 (83%) had a *GNAS*-mutation. All mutations were found on exon-8; in 4 cases codon 201 was bearing the R201H mutation and one case showed a R202C mutation localized in codon 202. In none of these patients material was available from bony fibrous dysplasia lesions to determine whether mutations of the bony lesions matched those of the soft tissue myxomas.

DISCUSSION

In this European multicentre study we evaluated the prevalence and clinical characteristics of Mazabraud's syndrome in one of the largest cohorts of patients studied to date, including series of patients from 6 European centres. Identifying only 32 patients, representing a prevalence of 2.2%, confirms the very rare nature of this syndrome. Our data also suggest that the syndrome is more common in women (ratio 2.2:1) and in

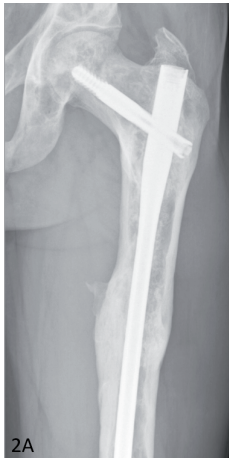
Table 5.2 Patient characteristics

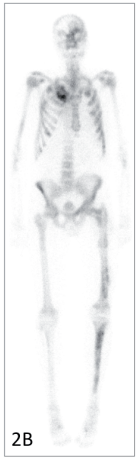
Patient ID	Gender	Type of FD*	Localization FD	Age diagnosis FD	Localization myxomas**	Age at diagnosis myxomas	Number of myxomas	Symptoms myxomas	GNAS-mutation in the myxoma	Follow-up in years
1	Male	PFD	Humerus + femur + pelvis	14	LD	19	1	Swelling	NT	41
2	Female	PFD	Ribs	61	Tr + QL	61	1	None	NT	6
3	Female	PFD	Femur + tibia + pelvis	32	Q + HA	45	8	Pain	R201H	20
4	Male	PFD	Femur + tibia	39	Q + HA + H	39	5	Swelling	No mutation	16
5	Female	PFD	Sternum + femur + pelvis + tibia + fibula	16	Q + HA	46	3	Swelling	R201H	51
6	Male	PFD	Craniofacial + humerus + ribs + pelvis + femur + tibia	38	Q + GM + HA + PM	52	20	Pain	R201H	14
7	Male	PFD	Femur + pelvis + tibia	23	Q + PM	31	1	Pain	R202C	19
8	Female	PFD	Femur + humerus	49	HA + Tr	49	5	Pain	-	2
9	Female	MAS	Ribs + pelvis + femur + tibia	50	Q	50	3	None	R201H	2
10	Female	MAS	Craniofacial + humerus + radius + ribs + spine + pelvis + femur + tibia	0	GM + HA	41	5	None	NT	41
11	Male	MFD	Femur	55	Q	56	1	None	NT	1
12	Female	MFD	Femur + tibia	48	Q	48	1	None	NT	4
13	Female	MFD	Femur	40	Q	40	1	Swelling	NT	1
14	Female	MAS	Craniofacial + humerus + ribs + spine + pelvis + femur + tibia + fibula	0	Qs + HA + GM	43	8	Pain	NT	1
15	Female	MAS	Craniofacial + ribs + pelvis + femur + tibia	19	Q + GM	32	3	Pain	NT	23
16	Female	PFD	Femur + tibia	52	GM	54	3	Pain	NT	13

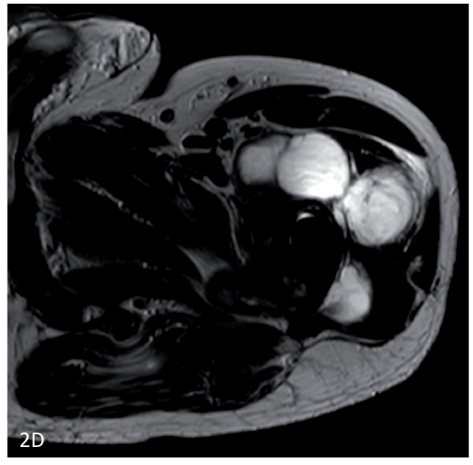
Table 5.2 *Continued*

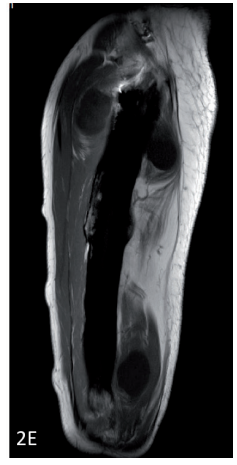
Patient ID	Gender	Type of FD*	Localization FD	Age diagnosis FD	Localization myxomas**	Age at diagnosis myxomas	Number of myxomas	Symptoms myxomas	GNAS-mutation in the myxoma	Follow-up in years
17	Male	PFD	Femur + tibia	51	Q	51	1	Pain	NT	1
18	Female	PFD	Femur + tibia	15	Q	31	1	Swelling/pain	NT	26
19	Male	PFD	Femur + pelvis	63	GM	62	1	Pain	NT	7
20	Male	PFD	Femur + pelvis	49	HA	49	3	Swelling	NT	0
21	Male	PFD	Femur + pelvis + tibia	35	Q	42	1	None	NT	8
22	Female	PFD	Femur + pelvis + tibia	23	Ga	29	1	Pain	NT	9
23	Female	MFD	Femur	65	Q	65	1	Pain	NT	5
24	Female	PFD	Humerus	56	Tr	56	1	Pain	NT	0
25	Female	PFD	Femur	60	Q + PM	56	3	Pain	NT	16
26	Male	PFD	Craniofacial + femur + talus	22	HA	61	1	Pain	NT	47
27	Female	PFD	Femur + fibula	13	Q	54	1	Pain	NT	44
28	Female	PFD	Femur + tibia	40	Q	40	1	Pain	NT	11
29	Female	PFD	Femur + pelvis + tibia	10	Q + HA + Ga	36	8	Pain	NT	11
30	Female	MAS	Craniofacial + ribs + pelvis + femur + tibia	18	Q + HA	40	4	Pain	NT	17
31	Female	PFD	Femur + tibia	70	Q	70	3	Pain	NT	11
32	Female	MFD	Humerus	69	GM + LD	69	2	Pain	NT	2

* MFD = monostotic fibrous dysplasia; PFD = polyostotic fibrous dysplasia; MAS = McCune-Albright Syndrome.
** LD = latissimus dorsi; Tr = triceps; QL = quadratus Lumborum; Q = quadriceps; HA = hip adductors; H = hamstrings; GM = gluteus maximus; PM = psoas major; Ga = gastrocnemicus.
*** Exact localisation of the myxoma is unknown.
NT = not tested.









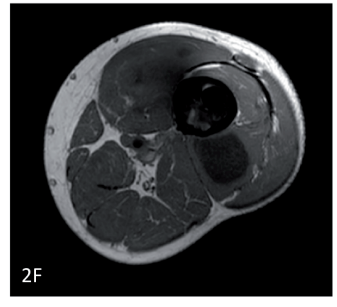


Fig. 5.2 Illustrative case of Mazabraud's syndrome. Images of a male patient (ID 6) with polyostotic FD of the craniofacial region, humerus, ribs, pelvis, femur and tibia, predominantly located on the left side of the body. He first presented with a fracture of the left femur at the age of 11 years, for which he was twice treated with an osteosynthesis. The diagnosis of FD was not made until he was 38 years old and had a recurrence of the femoral fracture for which he was treated with a long intramedullary nail. He was lost to follow-up and presented 15 years later at the age of 52 years to the outpatient clinic with progressive pain in the left upper leg during walking and cycling. Physical examination revealed a swelling in the region of the vastus lateralis. An X-ray of the femur and a T99m-skeletal scintigraphy (Fig. 5.2A and 5.2B) showed no changes in the size or appearance of the bony femoral FD lesions and no complications associated with the angled blade plate. A subsequent MRI investigation (Fig. 5.2C and 5.2D) showed 20 round, well-defined lesions within the muscles of the gluteus, quadriceps, hip adductors and ileopsoas, suggesting a diagnosis of Mazabraud's syndrome and pointing the soft tissue lesions as source of the exercise-related complaints. Three of the soft tissue tumors located proximally in the vastus lateralis who were believed to cause most of the complaints were resected and confirmed on histopathological evaluation to be mutiple intramuscular myxomas of low cellularity. Genetic analysis of the myxomas revealed the presence of a GNAS-mutation (A201H). On return to the out-patient clinic three months postoperatively the patient free of pain during exercise and could fully enjoy cycling and walking again. Unfortunately, two years later he presented again with complaints of pain in the region of the distal femur. MRI (Fig. 5.2E-F) showed growth of previously seen lesions on the posterior side of the distal femur, but no recurrence in the area of the resected myxomas. Because his complaints were mainly located on the anterior side, we chose a wait-and-see policy, as the complaints might also be caused by tissue fibrosis in that region. The patient is currently closely monitored with a view to timely resection of symptomatic lesions when required.

Table 5.3 Outcomes of surgery (total number of patients: 22)

Patient ID	Reason for surgery	Free margins	Cellularity	Recurrence of myxoma	Reoperation ()	Number of resections	Complications
3	Pain	Yes	Poor	No	No	1	None
4	Pain	Yes	High	Yes	Yes	2	None
5	Pain	Yes	-	No	No	1	None
6	Pain	Yes	Poor	No	No	1	None
7	Diagnosis	Yes	High	Yes	No	1	None
12	Diagnosis	Yes	Poor	No	No	1	None
14	Pain	Yes	Poor	No	No	1	None
16	Pain	Yes	High	No	No	1	None
17	Pain	Yes	Intermediate	Yes	No	1	None
18	Diagnosis	Yes	Poor	No	No	1	None
19	Pain	No	High	No	No	1	None
22	Pain	Yes	Poor	No	No	1	None
23	Pain	Yes	High	No	No	1	None
24	Pain	Yes	High	No	No	1	None
25	Pain	Yes	-	Yes	Yes	3	Delayed wound healing + temporary femoral nerve palsy
26	Pain	Yes	-	No	No	1	Delayed wound healing
27	Pain	Yes	High	No	No	1	None
28	Pain	Yes	High	Yes	Yes	2	None
29	Pain + diagnosis	Yes	High	Yes	Yes	2	None
30	Pain + diagnosis	Yes	Poor	No	Yes	2	None

Table 5.4 Results of mutation analysis in myxomas

Type of sequencing	Patient ID	Type of tissue	*GNAS*-mutation	Type	Reads	Frequency
Next generation sequencing	3	Myxoma	Positive	R201H	1364	12%
	5	Myxoma	Positive	R201H	1423	3%
	9	Myxoma	Positive	R201H	2144	3%
Sanger sequencing	4	Myxoma	Negative			
	6	Myxoma	Positive	R201H		
	7	Myxoma	Positive	R202C		

patients with polyostotic FD (ratio 5.4:1), and that myxomas are diagnosed at a later stage in the natural history of the associated skeletal fibrous dysplasia at a mean of 10 years after diagnosis of the latter (47.4 ± 12 years). Surgical resection of the myxoma(s) is associated with a good outcome, with disappearance of pain complaints in the majority of the patients, although recurrence is observed in 32% of cases, possibly related to high cellularity of the initially resected myxoma. Five out of the 6 myxomas genetically analysed were found to have a *GNAS*-hotspot mutation, confirming the shared genetic origin of fibrous dysplasia and intramuscular myxomas. In the sixth case only Sanger sequencing was performed, and since the percentage of cells with a mutation can be very low, as is evident from the tumors that were submitted for targeted NGS (Table 5.4), it can not be excluded that a mutation would have been found in case a more sensitive technique would have been used.

Mazabraud's syndrome has been previously reported to occur in approximately 1% of all cases of fibrous dysplasia.[8] However, Benhamou et al. recently reported a prevalence of 2.4% in a cohort of 372 patients with FD,[13] and we observed a combined prevalence of 2.2% in our study in a largest so far studied combined cohort of 1446 patients with fibrous dysplasia. This discrepancy in prevalence of the syndrome between studies might be at least partially accounted for by the more frequent use of magnetic resonance imaging (MRI) in FD as myxomas are not visible on plain radiographic imaging. It is likely, however, that our prevalence data may still represent an underestimate of the true prevalence of myxomas in patients with FD, as the majority of the intramuscular myxomas are likely to be asymptomatic and only patients with persistent and unexplained symptoms are likely to be referred for an additional MRI. Our data provide further evidence that myxomas may be the source of debilitating unexplained symptoms warrenting further analysis in patients with disproportional pain complaints, ununderstood functional limitations or resistance to treatment that

cannot be explained by findings from plain radiographs or T^{99}-skeletal scintigrams. Additional imaging should focus on the possibility of soft tissue pathology in the form of intramuscular myxomas, especially if the complaints are localized in the upper leg.

Clinical characterisics of Mazabraud's syndrome

Previous reviews suggest that the majority of patients with Mazabraud's syndrome have polyostotic forms of FD, two case reports mentioned linking the syndrome with the McCune-Albright syndrome.[14,15] Data from our combined European cohort suggest a higher prevalence of Mazabraud syndrome in patients with polyostotic fibrous dysplasia, especially those with the McCune-Albright syndrome (respectively 58% and 16%) compared to those with the more common monostotic type of FD (16%). The chance of developing myxomas appears thus to increase in the presence of the more severe types of fibrous dysplasia, possibly related to a higher tissue distribution of the *GNAS*-mutation not only in bone but also in soft tissues. A caveat to this premise is the finding in our study of 16% of patients with Mazabraud syndrome having monostotic fibrous dysplasia suggesting that soft tissue myxomas may also develop in the milder types of fibrous dysplasia and warranting further investigations for unexplained symptoms also in this group of patients.

In keeping with previous reports, myxomas in our cohort were mostly located in the upper leg and in nearly all were located nearby a bony FD lesion.[10,16] Intrestingly, the bony lesions in fibrous dysplasia also have a preference for the upper leg with most lesions found in the proximal femur.[17] *GNAS*-mutations have been identified in fibrous dysplasia lesions as well in intramuscular myxomas, suggesting a likely common causative mechanism.[3,4] *GNAS*-mutations have been indeed shown to play an important role in the development of extra-skeletal manifestations other than myxomas in patients with fibrous dysplasia.[12,18] With 83% of samples analysed in the current study showing this mutation in intramuscular myxomas, this shared origin is further confirmed. As the only myxoma lacking a *GNAS*-mutation reported here was solely analysed with Sanger Sequencing, the mutation rate in our study could even have increased up to 100% if analysis of this myxoma would have been repeated with the more sensitive Next Generation Sequencing technique.

Contrary to previous reports suggesting an increased risk of malignant transformation of bony fibrous dysplasia lesions in Mazabraud's syndrome, none of the patients studied in this combined cohort had evidence for malignant transformation of either a bony FD lesion or a myxoma.[10,19]

Surgical resection of myxomas in Mazabraud's syndrome

Surgical resection of symptomatic myxomas has been reported to be successful in relieving pain symptoms in patients with Mazabraud syndrome.[9,20] However, myxomas have a tendency to recur in the Mazabraud syndrome compared to simple intramuscular myxomas.[21] This was further emphasized in our study by the 26% of patients who were treated with a resection of a myxoma having to undergo further surgery for a recurrence despite having evidence for clear margins of the initially resected lesion. The World Health Organisation describes myxomas as benign soft tissue tumours that consist of bland spindle shaped cells in a matrix of myxoid stroma.[21] So-called 'cellular myxomas' demonstrated increased cellularity, collagen fibres and blood vessels and was described to have an increased risk of local recurrence.[22] Our data suggest that also in Mazabraud syndrome an increased risk of recurrence is seen in tumors in which the pathologists report increased cellularity. However, caution should be exerted in the interpretation of these data with care because of the difficult distinction between the recurrence of a specific resected myxoma and newly developed myxomas in patients with multiple myxomas, as is possible in Mazabraud's syndrome. Another reservation with the interpretation of the role of cellularity of myxomas in the prediction of recurrence in our study is that data on cellularity was extracted from histological reports produced by local pathologists from the 6 different centres taking part in the study, rather than being centrally evaluated, and therefore interobserver variability will exist. This also applies to the evaluation of free resection margins.

Similarities and differences between solitary intramuscular myxomas and myxomas in the context of Mazabraud's syndrome

Our data confirm that similar to published data about solitary myxomas, myxomas in the Mazabraud syndrome are more prevalent in women, have a mean age of diagnosis of about 50 years and are predominantly located in the upper leg.[22,23] The *GNAS*-mutation that causes fibrous dysplasia has been identified in both solitary myxomas and myxomas in the context of Mazabraud's syndrome, suggesting a linked origin.[4] However, there are also differences between solitary intramuscular myxomas and myxomas in the context of Mazabraud's syndrome. Recurrence rates have been reported to be very low after resection of solitary myxomas, compared to several case-reports and data from our study showing recurrence and need for further surgery in myxomas of the Mazabraud syndrome.[22,24] Whether the high recurrence rate observed in the Mazabraud syndrome is due to the presence of multiple myxomas developing at different rates as also shown in our study, or whether histological characteristics

of the myxomas such as high cellularity may be responsible for the higher recurrence rate after resection remains to be established.[22,23]

In conclusion, this is the first study in which the prevalence and clinical characteristics of the very rare Mazabraud's syndrome could be evaluated in a relatively large combined cohort of patients from 6 European centres. It provides an ideal example of how international collaboration and multicentre studies provide a unique opportunity for investigating extremely rare entities, such as the Mazabraud syndrome.. Our data underline the importance of further evaluation of FD patients with disproportional complaints or uexplained resistance to treatment for the presence of soft tissue lesions at their source, also in patients with the milder monostotic forms of FD. Based on these findings, we recommend that all patients with FD regardless of type with inappropriately severe unexplained symtoms may be investigated for the presence of myxomas and offered resection to alleviate their symptoms. Our data further suggest that high cellularity of a myxoma in Mazabraud's syndrome is associated with increased risk of local recurrence and therefore may require closer monitoring.

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