Deep-seated ordinary and atypical lipomas

HISTOPATHOLOGY, CYTOGENETICS, CLINICAL FEATURES, AND OUTCOME IN 215 TUMOURS OF THE EXTREMITY AND TRUNK WALL

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Deep-seated lipomas are often atypical histologically and are considered by some to have a high risk of recurrence after excision. We reviewed 215 deep-seated lipomas of the extremities and trunk wall with reference to histology, cytogenetics, clinical features and local recurrence. We classified tumours with atypical features and/or ring chromosomes as atypical lipomas. These were more common in men, larger than ordinary lipomas and more often located in the upper leg. The annual incidence was estimated as ten per million inhabitants and the ratio of atypical to ordinary lipomas was 1:3. In total, six tumours (3%), recurred locally after a median of eight years (1 to 16); of these, four were classified as atypical.

The low recurrence rate of deep-seated lipomas of the extremity or trunk wall, irrespective of histological subtype, implies that if surgery is indicated, the tumour may be shelled out, that atypical lipomas in these locations do not deserve the designation well-differentiated liposarcoma, and that routine review after surgery is not required.

Lipomas are the most common soft-tissue tumours and may appear at any site. The usual presentation is as a solitary, slow-growing and painless subcutaneous tumour in the extremity or the trunk in an adult. Deep-seated, intra- and extra-muscular lipomas are less common and are larger than subcutaneous lipomas.¹ Some lipomatous tumours, mostly deep-seated in origin, are atypical histologically and are referred to as atypical lipomas, atypical lipomatous tumours, or well-differentiated liposarcomas. However, they have almost no potential to metastasise when they appear in the extremity or wall of the trunk, although dedifferentiation to a high-grade malignant sarcoma with metastatic potential has been described^{2,3} more commonly in retroperitoneal cases. Tumours in this location also have a high rate of uncontrollable local recurrence because of the difficulty in their complete removal. In 1988, Evans⁴ suggested that atypical lipomatous tumours should be called atypical lipomas when they appeared in the subcutaneous layer, or deep soft tissue and well-differentiated liposarcomas when they occurred retroperitoneally. The latest World Health Organisation classification of soft-tissue tumours adheres to this recommendation, but uses the term atypical lipomatous tumour instead of atypical lipoma.⁵

Like ordinary lipomas, atypical lipomas show a high degree of adipocytic differentia-

tion. However, the atypical variety has variability in the size of the adipocytic vacuole, shows more pronounced lobularity, has prominent collagen-rich septae, stromal cell nuclei with atypical features, and sometimes occasional lipoblasts are seen. Mitoses are rare or absent.⁶⁻⁸ The cellular atypia may sometimes be minimal and in such cases cytogenetic analysis might be helpful.^{3,9,10} Chromosomal analyses have shown that most atypical lipomas harbour ring chromosomes and/or giant marker chromosomes, which are uncommon in ordinary lipomas.^{2,10,11}

We have not found any studies assessing the incidence of atypical lipomas. Therefore, the incidence of this tumour and the ratio between ordinary and atypical deep-seated lipomas are unknown. It is unclear whether the differential diagnosis between an ordinary lipoma and an atypical lipoma is of clinical interest for tumours of the extremities or trunk wall. It has been suggested that atypical lipomas at these locations have a significant risk of recurrence after excision compared with ordinary lipomas^{3,4,6,7,12,13} and should be removed *en bloc* surrounded by a layer of normal tissue, to decrease the risk of local recurrence.^{7,8,13,14}

We assessed the incidence of atypical and ordinary lipomas, their local recurrence rates, and the relationship between atypical histological features, chromosomal aberrations and

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clinical features in a series of 215 deep-seated lipomas of the extremities and trunk wall.

Patients and Methods

Our patients had been referred to the Orthopaedic Oncology Group in Lund before surgery. Referral was according to our guidelines for the management of patients with deep-seated soft-tissue tumours or subcutaneous tumours larger than 5 cm, which recommends referral to our centre before surgery because of the high risk of sarcoma developing in such lesions.¹⁵ Our unit serves a population of 1.5 million in southern Sweden. We included 213 patients, of whom two had two tumours each, with a primary, deep-seated lipoma located in the extremities or wall of the trunk and operated on between January 1983 and May 2006. The surgery and histopathological analysis were performed at the Departments of Orthopaedics and Pathology at the University Hospital in Lund, respectively. The study was approved by our institutional review board.

The mean age of the patients was 56 years (10 to 94) and 107 were women. The most common site was the upper arm (62), including the shoulder girdle, followed by the upper leg, including the thigh (62), groin and buttock, the trunk wall (40), the lower arm (29) and the lower leg (15). The location was unknown in seven patients. The median size of the tumour was 8 cm (2 to 28). The histopathological diagnosis was an atypical lipoma in 38 tumours (18%) with the others all classified as an ordinary lipoma.

All the patients were operated on by dedicated orthopaedic tumour surgeons and all excision biopsies were examined by experienced musculoskeletal tumour pathologists, who were members of the Orthopaedic Oncology Group in Lund. Almost all patients had undergone surgery with a marginal surgical margin (shelling out). In a few patients, when the lipoma macroscopically infiltrated muscle tissue, a small rim of muscle was included *en bloc* with the tumour. A wide excision of the lipoma, completely surrounded by macroscopically healthy tissue, was only performed in two patients because of a large tumour in a small muscle. In one patient a 10 cm lipoma had occurred in the gracilis muscle and in the other a 5 cm lipoma in the sartorius muscle. No patient had any treatment other than surgery. Clinical data, including the surgical reports, were obtained from the medical records, which were available for all patients.

There had been no regular follow-up of the patients but they had all been instructed to contact the Department of Orthopaedics if they suspected a recurrence of their tumour. We contacted 178 patients (83.5%) by telephone and asked about symptoms which may have been created by a local recurrence, such as a new lump or swelling at the same site as the excised lipoma. We were unable to trace 13 patients and 22 had died. None of these 35 patients had contacted the Department of Orthopaedics since their lump had been excised, nor had any of them had a local recurrence or metastatic disease diagnosed at our Department of

Pathology. The mean follow-up time, excluding those patients who had surgery during 2006, was 9.5 years (1 to 23).

Cytogenetic analysis. Initially as part of a research project, and later as part of the diagnostic routine, a fresh biopsy of the excised lipoma was sent to the Department of Clinical Genetics, Lund University Hospital, for cytogenetic analysis. Culturing, harvesting, and G-banding were performed as described elsewhere.¹⁶ For the present study, the karyotypes were surveyed with regard to the presence of structural rearrangements of bands 12q13-15, supernumerary ring chromosomes and/or giant marker chromosomes ('rings'), and rearrangement or loss of chromosome arm 13q.

Statistical analysis. Statistical analyses were performed using the Fisher exact test (two-tailed) or the Mann-Whitney U test (two-tailed, without correction for ties) when appropriate. Statistical significance was set at $p < 0.05$.

Results

Two patients had two deep-seated lipomas. All four were ordinary lipomas histologically, and none recurred. As they showed distinct abnormal karyotypes, these four lipomas were considered independent tumours.

Cytogenetic analysis was performed in 192 tumours. Of these, in four tumours no mitoses were obtained, and a normal karyotype was found in 27. An aberrant karyotype was thus found in 161 (83%). Of the tumours with aberrations, 93 (58%) showed a structural rearrangement of 12q13-15, 44 (27%) had rings, and 19 (12%) showed rearrangement or loss of chromosome arm 13q. In 36 tumours (22%), other clonal chromosome aberrations were found. Of the 161 lipomas with karyotypic aberrations, 31 had atypical histological features and rings, 13 had rings but no atypical histological appearances and six had atypical histological features but no rings. These three groups shared similar clinical features, different from the 111 tumours without atypical histological appearances and no rings (Table I). Based on these observations, we decided to classify tumours with atypical histological features, irrespective of cytogenetic findings, and tumours with rings irrespective of histological findings as atypical lipomas ($n = 51$). All other tumours were classified as ordinary lipomas ($n = 164$).

In the total series of 215 tumours, the clinical features were similar in those in the subset of 161 tumours with karyotypic aberrations. Atypical lipomas occurred more commonly in men (35 of 51; two-tailed Fisher's exact test, $p = 0.002$) and were larger than the ordinary lipomas (median size 15 cm (5 to 28) *vs* 7 cm (2 to 28); two-tailed Mann-Whitney test, $p < 0.001$) and occurred most commonly in the upper leg (32 of 49 *vs* 30 of 159; two-tailed Fisher's exact test, $p < 0.001$).

The larger size of atypical lipomas could not be explained by their common location in the upper leg. Atypical lipomas in this location were larger (median size

Table I. The relationship between histology, cytogenetics and clinical features in 161 lipomas with karyotypic aberrations

Atypical histological features*	Rings	Number of tumours	Proportion of men (%)	Proportion located in upper leg (%)	Mean size in cm (range)
+	+	31	21 of 31 (67.7)	22 of 29† (75.8)	15.8 (6 to 28)†
+	-	6	5 of 6 (83.3)	3 of 6 (50)	15.4 (5 to 22)
-	+	13	8 of 13 (61.5)	6 of 13 (46.1)	14.7 (5 to 25)
-	-	111	57 of 111 (51.3)	23 of 107‡ (21.4)	9.4 (5 to 25)

*+, present; -, not present

† size not known for two lipomas

‡ location not known for four lipomas

Table II. The clinical and pathological data for six patients with local recurrence of their lipoma

Patient number	Time to recurrence (yrs)	Size of primary tumour (cm)	Size of local recurrence (cm)	Diagnostic method*	Histopathological diagnosis of the primary tumour	Cytogenetic subgroup
1	1	10	3	FNA	Atypical lipoma	Ring
2	4	8	5	MRI	Lipoma	12q
3	9	10	10	FNA, MRI	Atypical lipoma	Ring
4†	10	13	19	MRI	Atypical lipoma	Ring
5	16	5	5	FNA	Lipoma	Unknown
6	7	25	5	MRI	Atypical lipoma	Ring

* FNA, fine needle aspiration cytology

† surgery for local recurrence 16 years after primary operation

16.8 cm (5 to 27)) than ordinary lipomas in the same location (median size 10.9 cm (4 to 28) (Mann-Whitney U test, $p = 0.004$).

The annual incidence of deep-seated lipomas, both ordinary and atypical, requiring operation was seven per million inhabitants. The ratio of atypical to ordinary lipomas was approximately 1:3 (51:164).

The 35 patients who could not be contacted by telephone displayed features similar to those who could be contacted. Our Orthopaedic Oncology Group has been established for more than three decades, making it improbable that a recurrence in any of these 35 patients, treated at a local hospital, would not have been reported to us.

Overall, six patients (four men) had a local recurrence (3.3%). One of the tumours was situated in the upper arm and five in the upper leg. The size of the recurrence ranged between 3 cm and 19 cm. The histological diagnosis of the primary tumour was an atypical lipoma in four cases. Cytogenetic analysis of the primary tumour had been performed in five cases; one had aberrations involving 12q13-15 and four had rings (Table II). One patient underwent surgery for local recurrence during the time of the study. The primary tumour, as well as the recurrence, had been diagnosed as an atypical lipoma. The other five local recurrences were identified among the 178 patients who were interviewed by telephone. They reported symptoms that could have been attributable to a local recurrence, and were all recalled for a physical examination and, when considered appropriate, fine-needle aspiration cytology or MRI, which confirmed a local recurrence in four patients. A further patient underwent re-examination when he contacted us shortly after the initial interview. A local recurrence was found. The median

time between surgery and the recurrence was 7.8 years (1 to 16). The tumours had been slowly growing or, in some cases, had stopped growing.

Discussion

The two largest studies on atypical lipomas were by Bassett et al.³ and Sommerville et al.¹⁷ Like ours, the latter study was based on an unselected, consecutive series of 61 atypical lipomas, but did not include ordinary deep-seated lipomas, nor were cytogenetic results used in the diagnostic process. Bassett et al.³ in their study of 106 patients with deep-seated lipomas (55 ordinary, 51 atypical), took cytogenetic results into account when making the diagnosis of an atypical lipoma. However, in comparison with our approach, they put even greater emphasis on the karyotype and decided that a tumour, in spite of showing atypical histology, should be classified as an ordinary lipoma if it displayed karyotypic aberrations typical of this entity. The median follow-up time was longer in our series at 90 months than in the two previous ones at 61³ and 50¹⁷ months, respectively.

We found that 38 of the 215 tumours (18%) were atypical lipomas histologically. We acknowledge that the histology slides were not re-reviewed, but all tumours had been diagnosed by experienced musculoskeletal pathologists. Karyotyping was successful in 37 of these tumours and showed, in agreement with previous reports,¹⁰ rings in 30 (81%). However, rings were also found in 13 of 127 (10%) histologically ordinary lipomas from which abnormal karyotypes were available. These 13 patients displayed the same clinical features as histologically atypical lipomas, strongly suggesting that they were also atypical lipomas, although

the extent of atypical nuclear material may have been too subtle to be recognised on routine histopathological analysis, even when performed by experienced musculoskeletal tumour pathologists.¹⁰ Furthermore, the six tumours with atypical histology but with no rings showed the same clinical features. Based on the experience from cytogenetic analysis of other types of tumour, we think it unlikely that there should be a perfect correlation between morphology and cytogenetic profile. Thus, we considered it prudent to classify a lipoma as atypical when it showed atypical histological features and/or had rings at cytogenetic analysis.

Except for one previous study from our group,¹ we have been unable to identify any report on the incidence of lipomas in a defined population. In our previous work, which comprised histopathologically diagnosed lipomas during 1979 in a Swedish population of 750 000 inhabitants, 13 deep-seated lipomas were found.¹ This represents an annual incidence of 16 per million population, but no distinction was made between atypical and ordinary lipomas in that study. The annual incidence in the present series was seven per million. In our first report¹ the incidence may have been too high; classification of a deep-seated location was in some cases based on the histological finding of small areas of muscle tissue close to the tumour. In contrast, the incidence in the present series is probably too low as not all patients would have been referred to us for surgery. Especially during later years several deep-seated lipomas have been diagnosed by CT or MRI and fine-needle aspiration biopsy at local hospitals in our catchment area. Clinical data, radiographs and cytology smears have in most cases been sent to our tumour group for analysis. If we subsequently confirmed an ordinary lipoma, not all of these patients would be referred to us. In some patients, surgery has not been considered necessary and in a few patients small, easily excised tumours were removed at the local hospital. Taken together, we estimate that the annual incidence of patients seeking medical advice and being operated on for a deep-seated lipoma is about ten per million.

The ratio between a histologically atypical lipoma and an ordinary lipoma in the entire series was approximately 1:3. Since minor atypical features may have been histologically missed in some tumours, and 25% of the lipomas had either not been karyotyped or were cytogenetically not informative, it could be argued that additional cases with atypical features have been overlooked. Indeed, among the cases with abnormal karyotype, a ratio of approximately 1:3 was seen, but this is still lower than the 1:2 relationship reported by Bassett et al.³ This discrepancy might be because of differences in patterns of referral.

Clinically, atypical lipomas differed from ordinary lipomas. Approximately 65% of the atypical lipomas occurred in the upper leg compared with 20% of the ordinary lipomas, 83% of atypical lipomas were larger than 20 cm compared with 4% of ordinary lipomas; and they were more common in men. The larger size of atypical lipomas and their predilection for the upper leg has been previously

described,^{3,17} but none of these authors found any gender difference.

While the explanation for atypical lipomas being larger than ordinary lipomas might be that atypical lipomas are more commonly found in the thigh, it was found that atypical lipomas in the upper leg were larger than ordinary lipomas in the same location. Most lipomas are painless and incidentally observed by the patient.¹⁷ However, one can only speculate that a faster growth rate in atypical lipomas allows them to grow larger from the time of discovery to the time of excision.

We defined local recurrence as an enlargement in the area of the earlier excised lipoma, detected by the patient. It is possible that physical examination and MRI of all patients would have identified additional asymptomatic local recurrences. A local recurrence was found in six of the 178 patients contacted by telephone, of which four were atypical lipomas; only two patients had sought medical attention. This represents a local recurrence rate in an atypical lipoma of 4 of 51 (7.8%). Some authors have found similar rates,¹⁷ other reports have placed the rates at 27%³ and 52%.¹⁸

It has been suggested that atypical lipomas should be removed by a wide margin to reduce the risk of local recurrence¹³ but we found that a marginal resection was sufficient. It is possible that our low local recurrence rate may be a reflection of our patients all being operated on by a musculoskeletal tumour surgeon who removed the tumours *en bloc*, trying to maintain the integrity of the thin 'capsule' surrounding the lipoma. A less careful excision might result in higher local recurrence. Only two of the lipomas in our series were removed by a wide margin (myectomy) and in only a few macroscopically infiltrative tumours was a thin rim of muscle tissue removed, but this never completely surrounded the tumour. A similar low local recurrence rate (5 of 61; 8.2%) after shelling out of atypical lipomas in the extremities has been reported from another tumour centre.¹⁷ In their series, all patients attended for routine follow-up but the mean duration was only for four years (2 to 9). The authors speculated that the local recurrence rate would increase with longer follow-up.¹⁷

It is reasonable to question whether all deep-seated lipomas need to be removed. Sometimes, deep-seated lipomatous tumours seem to stop growing and give minor or no symptoms. A reliable diagnosis can be made by CT or MR imaging supported by needle biopsy.¹⁹

Long-term follow-up has been considered a requirement after surgery for an atypical lipoma in the extremities because of the risk of local recurrence and/or dedifferentiation.¹⁷ We do not agree with this view. A local recurrence will at some stage be identified by the patient and malignant transformation seems to be extremely rare, not occurring in our series. Furthermore, it has been shown that most local recurrences after treatment of soft-tissue sarcomas of the extremities are noticed by the patient before it is diagnosed by a doctor at a routine review.²⁰

We conclude that approximately 25% of deep-seated lipomatous tumours in the extremity or wall of the trunk are atypical lipomas. They are often diagnosed by ordinary histopathological examination but in some patients only chromosomal aberrations may confirm the diagnosis. They are larger than ordinary deep-seated lipomas and occur most commonly in the upper leg and have a higher rate of recurrence than ordinary lipomas. Nevertheless, the local recurrence rate remains low, in our series 7.8%, even after a marginal resection and long follow-up. Dedifferentiation to a highly malignant sarcoma in these tumours seems to be extremely rare. Our findings confirm that it is reasonable, if surgery is indicated for a deep-seated lipomatous tumour of the extremity or trunk wall, to excise it with marginal margins (shelling out). Additionally, atypical lipomas in these locations do not deserve the designation well-differentiated liposarcoma, and routine control after surgery does not seem to be warranted.

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