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Cutaneous leiomyomas and leiomyosarcomas: an immunohistochemical study with p53

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Abstract

Background: Cutaneous smooth muscle tumors are rare and sometimes the differential diagnosis between leiomyoma and leiomyosarcoma is difficult and based in very subtle criteria. We therefore tried to investigate the use of p53 in such a conundrum. This marker has rarely been reported in cutaneous leiomyomas and even in more rare occasions, in cutaneous leiomyomas. *Material and Methods*: We studied 30 benign cutaneous smooth muscle tumors, including angioleiomyomas, common leiomyomas and a symplastic leiomyoma, as well as four leiomyosarcomas and one cutaneous metastasis of leiomyosarcoma. All cases were reviewed in order to confirm the diagnosis, before the cases were included in the study. In all cases, we performed an immunohistochemical study in all cases with p53 and the percentage of positive cells was estimate counting a total of 1000 cells per case. *Results*: Six cases from the 31 (19.35%) benign cutaneous smooth muscle tumors showed some expression of p53. The expression of it varied from only occasional cells to 1% of the cells. On the contrary, all leiomyosarcomas investigated showed expression of p53, and in three of the four cases (75%), the marker was expressed by at least 80% of the tumoral cells. Only in one leiomyosarcoma, the marker was expressed by a low percentage (0.5%) of cells. No expression of p53 was found in the only case of symplastic leiomyoma, which was investigated. The case of a cutaneous metastasis of leiomyosarcoma showed expression of p53 by 20% of cells. *Conclusions*: We conclude that expression of p53 by a high percentage of cells in a cutaneous smooth muscle cell tumor should be considered as highly suspicious for malignancy.

***Keywords*:** cutaneous leiomyosarcoma, p53, cutaneous leiomyoma, CD74.

Introduction

Cutaneous smooth muscle tumors are rare and sometimes the differential diagnosis between leiomyoma and leiomyosarcoma is based on subtle criteria, which do not have complete acceptance in literature, such as very few mitoses. Such a differential diagnosis, in smooth muscle tumors of other locations of the body, has sometimes relied upon immunohistochemical markers, for example, p53. Nevertheless, the studies on p53 and cutaneous smooth muscle tumors are not many [1, 2], and the ones studying the expression of p53 by leiomyomas are even less [3]. We, therefore, found it interesting to investigate this marker by immunohistochemistry in cases of angioleiomyomas, common leiomyomas, symplastic leiomyomas, leiomyosarcomas and a cutaneous metastasis of leiomyosarcoma.

Material and Methods

We studied 35 cases from our archives: 21 angioleiomyomas; eight common leiomyomas; one symplastic leiomyoma; four leiomyosarcomas; and one cutaneous metastasis of leiomyosarcoma. The case of the symplastic leiomyoma had previously been reported as a single case [4]. All cases were reviewed in order to confirm the diagnosis, before the cases were included in the study. We admitted a diagnosis of smooth muscle tumor, not only when the morphology of the tumor suggested so, but also when there was expression of smooth muscle actin. The criteria, which were used in order to consider a cutaneous smooth muscle tumor as a leiomyosarcoma, were: a mitotic rate of two or more mitoses per 10 high power field (HPF) [2] or presence of necrosis [5]. Atypia on its own was not considered as a definite diagnostic feature of leiomyosarcoma, unless accompanied by either of the two former criteria.

The clinical history of all patients was also reviewed, in order to know the evolution of the lesions after they had been excised. The times of follow-up were also checked.

We performed an immunohistochemical study in all the cases with p53 (DakoCytomation, monoclonal mouse anti-human p53 protein; clone DO-7; code N1581; ready to use). We used the Autostainer Link 48 (Dako). The biopsies were exposed to the EnVision™ FLEX Target Retrieval Solution (Dako) of high pH (9) for 20 minutes at 95^0C.

The percentage of positive cells was estimated, counting 1000 cells per case.

Results

Table 1 shows the details about the cases that were studied, including the immunostaining results. In those cases, in which p53 was expressed, the table also shows the percentage of positive cells.

Only six out of the 31 (19.35%) benign cutaneous smooth muscle tumors showed some expression of p53 (four angioleiomyomas and two common leiomyomas). The expression of this varied from only occasional cells to 1% of the cells (Figure 1, left). On the contrary, all leiomyosarcomas investigated showed expression of p53, and in three of the four cases (75%), the marker was expressed by at least 80% of the tumoral cells

(Figure 1, right). Only in one leiomyosarcoma, the marker was expressed by a low percentage (0.5%) of cells. No expression of p53 was found in the only case of symplastic leiomyoma, which was investigated. The case of a cutaneous metastasis of leiomyosarcoma showed expression of p53 by 20% of cells.

Table 1 – ***Details about the cases that were studied***

Case no.	Gender	Age [years]	Diagnosis	p53 [% of cells]	Follow-up [months]	Patient's status
1.	M	25	Angioleiomyoma	-	4	A, NR
2.	M	63	Angioleiomyoma	-	6	A, NR
3.	F	65	Angioleiomyoma	-	6	A, NR
4.	F	68	Angioleiomyoma	-	6	A, NR
5.	F	57	Angioleiomyoma	+ (1%)	8	A, NR
6.	M	80	Angioleiomyoma	-	15	A, NR
7.	F	79	Angioleiomyoma	-	15	A, NR
8.	F	56	Angioleiomyoma	+ (0.5%)	22	A, NR
9.	M	49	Angioleiomyoma	-	65	A, NR
10.	F	46	Angioleiomyoma	-	29	A, NR
11.	F	78	Leiomyoma	+ (1%)	31	A, NR
12.	M	48	Angioleiomyoma	-	33	A, NR
13.	F	35	Angioleiomyoma	-	33	A, NR
14.	F	37	Angioleiomyoma	-	44	A, NR
15.	M	69	Angioleiomyoma	-	53	A, NR
16.	M	40	Angioleiomyoma	-	58	A, NR
17.	F	67	Angioleiomyoma	-	62	A, NR
18.	M	23	Angioleiomyoma	+ (only occasional cells)	68	A, NR
19.	F	73	Leiomyoma	-	68	A, NR
20.	F	54	Leiomyoma	+ (1%)	71	A, NR
21.	F	81	Leiomyoma	-	76	A, NR
22.	F	61	Leiomyoma	-	78	A, NR
23.	F	40	Leiomyoma	-	81	A, NR
24.	F	79	Angioleiomyoma	+ (0.5%)	88	A, NR
25.	F	72	Leiomyoma	-	88	A, NR
26.	F	74	Angioleiomyoma	-	89	A, NR
27.	F	66	Leiomyoma	-	95	A, NR
28.	F	73	Angioleiomyoma	-	98	A, NR
29.	F	73	Angioleiomyoma	-	98	A, NR
30.	F	32	Leiomyosarcoma	+ (0.5%)	9	A, NR
31.	M	76	Metastasis of leiomyosarcoma	+ (20%)	53	A
32*.	M	32	Symplastic leiomyoma	-	90	A, NR
33.	F	59	Leiomyosarcoma	+ (80%)	29	A, NR
34.	M	44	Leiomyosarcoma	+ (80%)	11	A, NR
35.	M	85	Leiomyosarcoma	+ (95%)	15	A, LR

A: alive; LR: local recurrence; NR: No recurrence. *This case was published before [4].

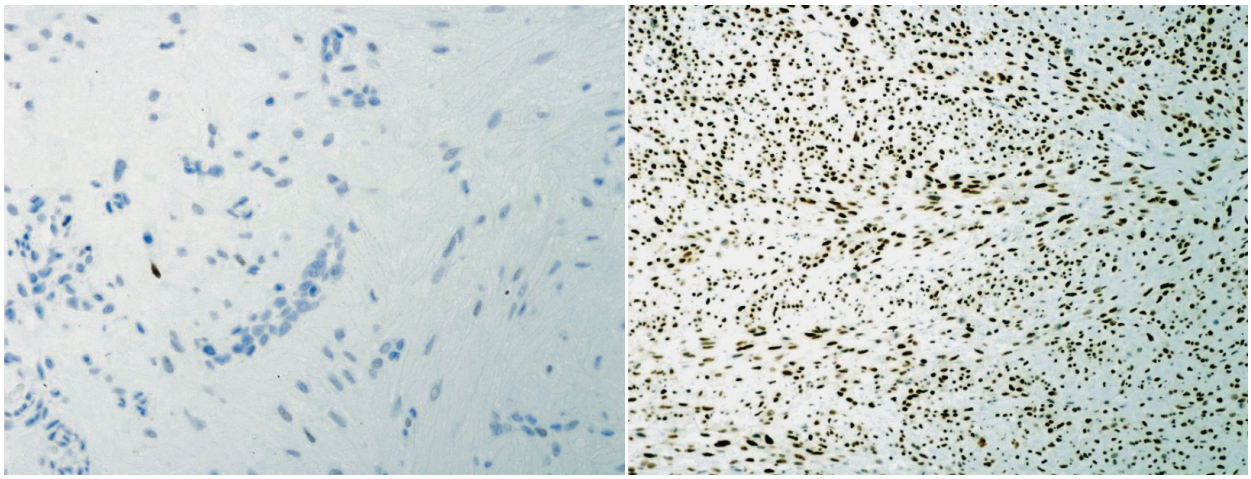

Figure 1 – ***Immunohistochemical expression of p53 by one of the leiomyomas (top; case no. 11), as well as by one of the leiomyosarcomas (bottom; case no. 35). While only occasional cells could be seen in some of the leiomyomas, leiomyosarcomas showed intense positivity in the majority of the cells.***

Discussion

In general pathology, some immunohistochemical markers have been used in the past in the differential diagnosis between leiomyosarcoma and leiomyoma.

CD74 [6] and p53 were two of the most studied markers. The latter was considered especially useful, so much so, that it was claimed how its expression by a smooth muscle tumor was suggestive of leiomyosarcoma. This was specially referred to smooth muscle tumors from the uterus [7–10], or the adrenal gland [11].

Such a claim, obviously, had many obligatory remarks. The expression of p53 by uterine leiomyosarcomas is not uniform [12], and some variants, such as the myxoid one [13, 14] have completely failed to express any p53 at all. Moreover, p53 positivity in common uterine leiomyosarcoma has not been a constant [15, 16], and some have demonstrated how mitotic rate had a higher significance than p53 immunostaining in prognostic terms for uterine smooth-muscle tumors [17].

Regarding cutaneous pathology, p53 has hardly ever been investigated in primary cutaneous smooth muscle tumors. Bellezza G *et al.*, for instance, investigated the marker in a group of seven cutaneous leiomyosarcomas [2]. Out of these, p53 was expressed by three cases, and the percentage of expression was 60%, 70% and 90% respectively. The other four cases failed to express the marker, which implies caution in terms of considering p53 as the only diagnostic clue of leiomyosarcoma when facing an otherwise innocent looking cutaneous smooth muscle tumor. On the other hand, it is very interesting, how out of the three cases which expressed p53 in Bellezza's series, two of them recurred (after 10 and 49 months) while only one out of the four cases, which were p53-negative, recurred.

Konomoto T *et al.* [18] studied 15 "superficial" leiomyosarcomas (meaning an origin not only from cutis, but also from subcutis and skeletal muscle) and they found immunoexpression of p53 by three of them ("over half of the nuclei" in two cases, and "a few scattered p53-positive nuclei" in the other one). These three patients were death after 12, 53 and 41 months of follow-up.

O'Reilly PE *et al.* also studied one case of leiomyosarcoma of the skin and did not find any expression of p53 [1]. Other series of extrauterine leiomyosarcomas have not included any primary cutaneous leiomyosarcoma at all [19].

p53 has even been studied less in cutaneous leiomyoma. Kawagishi N *et al.*, for instance, reported two cases of pleomorphic angioleiomyoma, which expressed p53 (by "many tumor cells" in their case no. 1 [in which a picture is also shown] and by "some of the large pleomorphic nuclei" in case no. 2) [3]. The authors had a follow-up of their two patients of up to two years, with no evidence of recurrence. Nevertheless, it should be mentioned how a minimal period of five years of follow-up is adequate when facing cutaneous smooth muscle tumors [20]. Contrary to what Kawagishi N *et al.* found, one of our cases (number 32) was symplastic, but we did not find any expression of p53, even by the pleomorphic cells.

Therefore, our studies corroborate the one of Bellezza G *et al.*, indicating that a high expression of p53 (equal or over 60%), in a primary cutaneous smooth muscle tumor, is highly suspicious of leiomyosarcoma. It also supports the concept that p53-negativity in a cutaneous smooth muscle tumor does not guarantee benignancy, as some others previously suggested [1, 2].

Nevertheless, it might be questioned if a smooth-muscle tumor that shows no worrying morphologic signs, apart from the positivity for p53, is a leiomyoma or a sarcoma. For instance, in gynecologic pathology, some uterine smooth-muscle tumors with a benign appearance, but which have expressed p53, have behaved as metastasising [21]. One wonders therefore, if this same feature would be applicable to skin pathology. Apart from the previously mentioned report on pleomorphic smooth muscle tumors of the skin [3], studies on p53 and cutaneous leiomyomas are not common in literature.

In this sense, our study contributes to fill that hole in literature.

None of our morphologically benign cases expressed p53 in a percentage superior to 1%. Even the ones expressing p53 in such a low percentage, did not show any malignant behavior (either as recurrent or metastasizing) in the follow-up periods that are shown in Table 1.

Therefore, according to our results, p53 could be useful as a complementary diagnostic tool when facing a cutaneous smooth muscle tumor. The diagnosis of such entities is not always easy and requires careful and wide examination. For instance, many admit that "a few" mitoses should be a worrying sign in well-differentiated lesions [22]. As few as one mitosis per 10 high-power fields (HPFs) can be observed in leiomyomas of arrector pili [23], but a mitotic rate in excess of 2/10 HPFs seems to be a good prediction of bad behavior [2, 20].

This is not, nevertheless, consensus [20], and some have remarked the failures in predicting malignancy when only based on mitotic rate [24]. One of the important things to remember is that cutaneous leiomyosarcomas may have "hot spots" of high mitotic activity [20], which does not rule out malignancy unless a thorough sampling of the lesion has been made [25].

That is why the presence of other criteria of malignancy in a certain biopsy, such as, for instance, a size greater than 5 cm [26, 27], is useful in supporting the diagnosis of malignancy.

Therefore, p53 could add some valuable information about the possible behavior of a certain lesion, according to the results presented in the current study: especially when positive in a high percentage of cells, in a non-symplastic leiomyoma, malignancy should be considered a priority.

Conclusions

We conclude that expression of p53 by a high percentage of cells in a cutaneous smooth muscle cell

tumor should be considered as highly suspicious for malignancy.

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