



Adrenal Involvement in Multiple Endocrine Neoplasia Type 1

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Abstract. Adrenal lesions belong to the spectrum of multiple endocrine neoplasia type 1 (MEN-1) syndrome. However, the prevalence of adrenal involvement, the characteristics, and the clinical management of adrenal lesions have not yet been clearly defined. A total of 66 patients with confirmed *MEN1* germline mutations and 1 additional patient with typical manifestations in three organ systems were monitored in a regular screening program that included evaluation of the adrenals (median follow-up 96 months; range 12 to 300 months). Age at the diagnosis of MEN-1 and of adrenal tumors and the clinical characteristics, genotype, treatment, and follow-up of adrenal disease were analyzed. Adrenal lesions were identified in 18 of 67 (26.8%) MEN-1 patients and were diagnosed 5 years later than MEN-1. The median tumor diameter at diagnosis was 3.0 cm (range 1.2–15.0 cm), with most tumors being 3 cm or smaller. Eight patients had bilateral tumors. Ten patients had nonfunctional benign tumors, three had benign adrenal Cushing syndrome, and one patient had a pheochromocytoma. Four patients developed adrenocortical carcinomas (ACCs), three of which were functional. Nine adrenalectomies and one subtotal adrenalectomy were performed in six patients. Three patients with ACC died owing to the tumor. Patients with mutations in exons 2 and 10 developed adrenal tumors significantly more often than patients with other mutations ($p < 0.01$). Adrenal tumors are a common feature of MEN-1 but occur later in the course of the disease. The lesions are often small and nonfunctional and can therefore be managed by close surveillance; others have significant malignant potential and should be considered for surgery when they are 3 cm or larger.

Multiple endocrine neoplasia type 1 (MEN-1) is classically characterized by the presence of neoplastic lesions of the parathyroid glands, the anterior pituitary gland, and the endocrine pancreas [1]. Neuroendocrine tumors (carcinoids) of the stomach, thymus, and lung as well as lipomas and ependymomas can also occur but are reported to be less common [2, 3]. Adrenal tumors associated with the MEN-1 syndrome were reported as early as the 1960s. Most of the first reports referred to autopsy studies or to incidental findings at laparotomy. Therefore the impact of adrenal involvement in the syndrome was underestimated [4]. In series

reported later the prevalence of adrenal involvement ranged from 9% to 41% [5–9]. Most of the lesions were described as nonfunctional. The major drawback of these studies was that the syndrome was diagnosed only clinically, so only clinical data could be evaluated. The genetic defect had not yet been identified. Therefore patients with only one organ affected and a negative family history were not included in these studies.

The *MEN1* gene has now been identified [10] and is located on chromosome 11q13 encoding a 2.8 kb protein of 610 amino acids, called menin. The exact function of menin is unknown, but there is some evidence that menin's tumor-suppressor function involves direct binding to the transcription factor JunD and inhibition of JunD activated transcription [11]. The *MEN1* gene now provides the basis for studies on the penetrance and spectrum of manifestations on genetically confirmed MEN-1 patients and mutation carriers. The aim of the present study was to determine the prevalence and clinical characteristics and the possible genotype/phenotype correlations of adrenal involvement in MEN-1 patients with confirmed germline mutations.

Patients and Methods

Patient Population

Patients with MEN-1 and mutation carriers were followed in an annual screening program in two German endocrine surgical referral centers. Altogether, 66 MEN-1 patients with confirmed *MEN1* germline mutations were monitored with biochemical and radiologic adrenal evaluations. One additional patient with typical manifestations of MEN-1 in the three typical organs was included in the study, but genetic analysis has not been completed. The median follow-up was 96 months (range 12–300 months). Age at diagnosis of MEN-1, age at diagnosis of adrenal involvement, clinical characteristics, treatment, and follow-up of adrenal disease as well as the possible genotype–phenotype correlation were analyzed. Adrenalectomy was performed when tumors were hormonally active or larger than 5 cm.

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Adrenal Evaluation

Adrenal involvement was evaluated clinically, biochemically, and radiologically. Nonfunctional hyperplasia or tumors were diagnosed if enlargement of the adrenal gland was confirmed on computed tomography (CT) or magnetic resonance imaging (MRI) scans in the absence of a clinical syndrome and adrenal hormone levels within normal limits. Adrenal Cushing syndrome was diagnosed when plasma cortisol levels were not suppressible by dexamethasone (overnight dexamethasone suppression test) and the ACTH level was suppressed. The diagnosis of pheochromocytoma was established when urine catecholamines (epinephrine > 109 nmol/day, norepinephrine > 620 nmol/day), vanillylmandelic acid (> 33 μ mol/day), or normetanephrines (> 1932 nmol/day) were elevated. Three cases of adrenocortical carcinoma (ACC), two cases of adrenal Cushing syndrome, two cases of nonfunctional adrenocortical neoplasia, and a pheochromocytoma were confirmed histologically.

Genetic Analysis

Mutation of the *MEN1* gene was analyzed as described previously [12, 13]. In brief, constitutional DNA was used for analysis of the nine coding exons of the *MEN1* gene by single-strand conformational variant analysis (SSCV) and direct sequencing. Sequencing was performed either with the SequiTherm kit (Biozym, Hessisch Oldendorf, Germany) or by Taq cycle sequencing using an automated sequencer (ABI 310 + 377 Genetic Analyzer, ABI-PRISM; Perkin Elmer, Foster City, CA, USA). *RET* proto-oncogene analysis was performed in the patient who presented with a pheochromocytoma [14].

Statistical Analysis

A *p* value < 0.05 was considered to indicate statistical significance.

Results

Adrenal Evaluation

Adrenal lesions were identified in 18 of 67 (26.8%) patients. This group consisted of nine women and nine men with a mean age of 51.2 years (36–70 years). The mean age at the diagnosis of MEN-1 in this group was 39.6 years (16–65 years). The mean age at the diagnosis of adrenal involvement was 45 years (18–65 years). Therefore adrenal involvement was diagnosed 5 years later than parathyroid or pancreatic endocrine lesions. In one patient adrenal disease was diagnosed prior to the first classic MEN-1 manifestation. Adrenal lesions were identified by CT in 13 cases, by MRI in 3 cases, and at autopsy in 2 cases. The median tumor diameter at diagnosis was 3.0 cm (range 1.2–15.0 cm) with 11 tumors being 3 cm or smaller. Four patients showed nonfunctional bilateral nodular hyperplasia. Three patients had adrenal Cushing syndrome due to bilateral adrenocortical hyperplasia, and one had a nonfunctional tumor on the right side and a nonfunctional ACC on the left side. Ten patients had unilateral adrenal involvement; among them, six tumors were nonfunctional, three patients developed unilateral hormonally active ACCs, and one patient had a pheochromocytoma. Nine adrenalectomies and one subtotal adrenalectomy were performed in six patients.

Histologic evaluation revealed macronodular hyperplasia of the adrenal cortex in two patients with bilateral adrenal Cushing syndrome. The adrenal cortex of the patient with pheochromocytoma also showed micronodular growth in addition to the typical appearance of a solitary pheochromocytoma in the medulla. In one patient with nonfunctional hyperplasia, histologic evaluation revealed nodular hyperplasia of the cortex and micronodular hyperplasia of the medulla. Three patients with ACC showed nodular and cystic formations, and normal adrenal tissue had disappeared.

In eight patients with nonfunctional tumors, lesions were observed with no change in function or size over a median period of 24 months (12–108 months). It is of note that two patients with initially diagnosed 2.5- and 5.0-cm nonfunctional lesions, respectively, developed large ACCs within 9 and 12 months, respectively.

At the conclusion of the study, six patients were alive with nonfunctional adrenal enlargement and one patient with adrenal Cushing syndrome due to bilateral adrenal enlargement, who has so far refused surgery. Five patients had no evidence of adrenal disease after adrenalectomy; three patients have died owing to their ACCs, and another three patients died owing to nonadrenal MEN-1-related manifestations.

Genetic Analysis

Among the 66 MEN-1 patients, 38 different *MEN1* germline mutations could be identified. The mutations were distributed throughout the gene. Altogether, 17 patients with adrenal involvement carried 15 different *MEN1* mutations that comprised 9 frameshift (P529X, K119X, K120X, E116X, W126X, M558X, E191X, Y90X, E530X), 3 missense (L168P, E26K, W436Y), 2 nonsense (E30X, Q64X), and 1 splice-site mutation (Table 1).

It is of note that 14 of 17 patients with adrenal involvement carried mutations in exon 2 or 10. A total of 36 patients with MEN-1 had mutations in exons 2 and 10. Fourteen of them (38%) had adrenal involvement, whereas only 3 of 30 patients with other mutations had adrenal tumors (Table 2). This difference was statistically significant (*p* < 0.01). One patient presenting with a histologically confirmed pheochromocytoma carried a germline *MEN1* frameshift mutation (K119X) and a wild-type sequence of the *RET* proto-oncogene.

Discussion

The present study on patients with genetically confirmed MEN-1 syndrome showed that adrenal tumors are a common feature of this syndrome. It occurs in about one-fourth of the patients. Reported series have been inconsistent regarding the prevalence of adrenal involvement in MEN-1 patients. It ranged from 9% to 40% (Table 3) [5–9, 15, 16]. Most of these studies could not be performed on patients with genetically confirmed *MEN1* germline mutations because the causative genetic defect had not been described. This is a possible reason for the marked variation in the reported prevalence of adrenal involvement in the MEN-1 syndrome. Another reason for possible underestimation of adrenal involvement are different screening protocols, which did not always include screening of the adrenals. Since the description of the *MEN1* gene, clinical algorithms in the follow-up of MEN-1 patients and mutation carriers have changed [17]. Screening has

Table 1. Characteristics of patients with genetically confirmed MEN-1 and adrenal involvement.

Patient	Gender	Age at Dx of MEN-1 (years)	Age at Dx of adrenal lesion (years)	Mutation exon/type	Adrenal tumor	Tumor diameter (cm)	Surgery	Follow-up regarding adrenals
1	M	41	48	2/K119X	Pheo, L	3.0	AE, L 05/93	NED
2	M	44	53	2/E116X	NF, L	1.7	None	AWD
3	M	43	48	2/E116X	NF, L	2.4	None	AWD
4	F	57	60	2/Y90X	NF, L	1.9	None	AWD
5	F	16	33	2/E30X	ACC, L	8.0	AE, L 01/92	NED
6	M	38	41	2/Q64X	NF, L	3.0	None	DUC
7	F	33	18	2/E191X	Cush, L	10.0	AE, L 1990	NED
					Cush, R	9.0	AE, R 1982	
8	F	25	32	2/K120X	ACC, R	7.0	AE, R 06/89	DOD
9	M	35	37	2/W126X	Cush, L	4.0	None	AWD
					Cush, R	4.0		
10	M	28	40	10/P529X	NF, B	NA	None	DUC
11	F	18	34	10/P529X	NF, L	2.0	None	AWD
					NF, R	1.8		
12	M	58	58	10/E530X	NF, R	1.9	AE, R 02/00	NED
13	F	65	65	10/M558X	NF, L	2.0	None	AWD
14	M	56	64	2/E26K	NF, B	2.0	None	DUC
15	F	37	38	I4/splise-site	Cush, L	4.0	AE, L 06/84 AE, R 07/85	NED
			40		Cush, R	3.5		
16	F	48	68	3/L168P	ACC, R	8.0	None	DOD
17	F	44	44	9/W436Y	NF, L	2.0	None	AWD
					NF, R	1.2		
18	M	26	34	?	ACC, L	15.0	AE, L + stAE 06/95	DOD
					NF, R	1.9		

NF: nonfunctional; Pheo: pheochromocytoma; ACC: adrenocortical carcinoma; Cush: Cushing tumor; B: bilateral; L: left; R: right; AE: adrenalectomy; stAE: subtotal adrenalectomy; AWD: alive with disease; DOD: dead of disease; NED: no evidence of disease; DUC: dead of unrelated cause; Dx, diagnosis; I4: intron 4; ?: unknown mutation; MEN-1: multiple endocrine neoplasia type 1; NA: not available.

Table 2. Distribution of MEN-1 mutations in patients with and without adrenal tumors.

Mutations	No. of patients with adrenal tumors/total (n = 66)	p (chi-square test)
In exons 2 + 10	14/36 (38%)	} < 0.01
In exons 3–9	3/30 (10%)	

Table 3. Frequency of adrenal tumors in MEN-1 patients (literature data).

Study	MEN-1 patients	
	Total	With adrenal tumors
Skogseid [9]	43	17 (40%)
Burgess [15]	33	12 (36%)
Carty [6] ^a	34	3 (9%)
Giraud [16] ^a	62	15 (24%)
Present study ^a	67	18 (26%)

^aGenetically confirmed.

become more thorough and is performed at shorter intervals, which obviously resulted in the detection of more adrenal tumors.

In only one of the patients in the present study was adrenal disease diagnosed prior to primary hyperparathyroidism, pituitary tumors, or pancreaticoduodenal endocrine tumors. On average, adrenal lesions occurred 5 years later than parathyroid or pancreaticoduodenal disease. Several clinical trials showed that the initial manifestation of MEN-1 is mostly primary hyperparathyroid-

ism or pancreaticoduodenal endocrine disease [6]. Nevertheless, it should be kept in mind that adrenal involvement belongs to the spectrum of MEN-1, and the family history should be evaluated carefully in patients with adrenal tumors. On the other hand, all patients with evidence of the MEN-1 syndrome should be screened for adrenal involvement.

Most of the adrenal lesions of the present study were nonfunctional hyperplasias or adrenal Cushing syndrome due to adrenocortical hyperplasia, which confirms previously reported data [8, 15]. However, four patients developed ACCs and one patient a histologically confirmed pheochromocytoma. The occurrence of pheochromocytoma as part of the MEN-1 syndrome is rare, ranging from 0 to 3% [6, 8, 15]. Some authors reported pheochromocytoma to be associated with pancreaticoduodenal endocrine tumors (PETs) as well as pituitary adenomas [18]. One patient with acromegaly, hyperparathyroidism, and pheochromocytoma has been described [19]. Some authors have speculated that the occurrence of these tumors apparently crosses syndrome lines between MEN-1 and, for example, MEN-2 or von Hippel-Lindau disease, therefore representing an endocrine neoplasia “overlap syndrome.” Recently, *MEN1* germline mutations were identified in two patients with pheochromocytomas [20]. The patient in the present study who had pheochromocytoma, insulinoma, prolactinoma, and primary hyperparathyroidism (pHPT) also carried a *MEN1*-germline mutation but wild-type sequences of the *RET* proto-oncogene. These data suggest that tumorigenesis of the pheochromocytoma was directly related to inactivation of the *MEN1* gene and that the clinical spectrum of MEN-1 therefore includes pheochromocytoma.

None of the patients of the present study was observed to have

an aldosterone-secreting lesion of the adrenals. Three cases of aldosterone-secreting adrenal tumors as a possible part of the MEN-1 syndrome have been reported in the literature [21–23]. Hence the MEN-1 syndrome may include the whole spectrum of adrenocortical and medullary pathology, but most of the adrenal lesions are nonfunctional hyperplasias and macronodular hyperplasias with adrenal Cushing syndrome, with a rather uneventful clinical course.

Bilateral adrenal tumor growth occurred in 8 of 18 patients (44%) in the present study; sporadic adrenal lesions mostly occur on one side only. Tumors of the classically affected organ systems of MEN-1 (e.g., endocrine pancreas and parathyroids) are characterized by multicentricity or multiglandular disease (or both). Available histology reports in the present study confirmed this also in the adrenals, as two patients with adrenal Cushing syndrome showed macronodular hyperplasia; and the patient with pheochromocytoma had micronodular changes of the adrenal cortex. Thus frequent bilateral occurrence of adrenal tumors and histologic signs of multicentricity add to the theory that adrenal tumors are primary lesions in MEN-1.

From the molecular biologic point of view, it remains unclear whether the development of MEN-1-related adrenal tumors is directly caused by inactivation of the *MEN1* tumor-suppressor gene. A Swedish group investigated 12 patients with adrenocortical tumors from 33 MEN-1 patients. They found loss of heterozygosity at chromosome 11q13 in only one ACC of a patient with MEN-1 but not in benign adrenal tumors of 11 other MEN-1 patients [8]. Several authors have reported series on genetic analysis of sporadic adrenocortical tumors. No mutations (somatic or germline) of the *MEN1* gene could be identified in those tumors [24–27]. Based on these molecular biologic observations, it was suggested that adrenocortical tumors may not be a primary lesion of the MEN-1 syndrome [28].

A recently reported large-scale study on MEN-1 patients showed no evidence of a genotype–phenotype correlation [16]. However, this study did not focus on adrenal tumors, and the authors grouped mutations into three classes: frameshift or nonsense mutations in exons 2 to 5, frameshift or nonsense mutations in exons 6 to 10, and missense mutations regardless of location in the gene. Our group recently described a potential genotype–phenotype correlation in MEN-1-related PETs [29]. Patients with truncating nonsense or frameshift mutations in the N- or C-terminal regions of the *MEN1* gene had a significantly higher rate of malignant PETs ($p < 0.02$) and tended to have shorter disease-free intervals than patients with other mutations. The present study also revealed that patients with mutations in exons 2 and 10 of the *MEN1* gene developed adrenal tumors (38%) significantly ($p < 0.01$) more often than patients with mutations in exons 3 to 9 (10%).

Based on these data one can hypothesize that MEN-1 patients with mutations in the N- or C-terminal region of the gene may have a more aggressive course of the disease, resulting in the development of more malignant tumors and more affected organ systems. Functional studies of the *MEN1* gene underscore this hypothesis, as it was shown that especially mutations in the N- or C-terminal region are important and may influence the course of the disease [30]. It could be demonstrated that the protein menin, encoded by the *MEN1* gene, functions as a transcriptional repressor through interaction with the transcription factor JunD. The interaction is mediated via the N-terminal transcription activation



Fig. 1. Magnetic resonance imaging (MRI) scan of patient P.K., a 70-year-old woman with a 2.5 cm nonfunctional adrenal tumor (August 1999).

Fig. 2. MRI scan of the same patient as in Figure 1, 9 months later (May 2000), now diagnosed with a hormonally active 8.0 cm stage IV adrenocortical carcinoma.

domain of JunD and the C-terminal part of menin. Therefore it seems to be worthwhile that mutations in the terminal regions of the *MEN1* gene could be important to the spectrum of manifestations of the disease. The observed genotype–phenotype correlation should be further evaluated in large-scale studies, as it would have clinical implications for screening strategies.

The malignant potential of the adrenal lesions in MEN-1 is striking. Four patients in the present study developed ACCs, which represent 6% of all MEN-1 patients and 22% of patients with adrenal involvement. Two patients developed large ACCs, one of them with lung and liver metastases, within 9 and 12

months after diagnosis of small nonfunctional adrenal enlargements, indicating dramatic malignant potential (Figs. 1, 2) [31]. Skogseid et al. reported a series of 43 MEN-1 patients, 17 of whom (40%) had adrenal involvement, and noted a similar observation [9]. The authors observed three patients with ACC, one of whom developed a 10 cm ACC within 13 months, with testosterone and estradiol excess. These data are alarming and strongly suggest that every nonfunctional adrenal enlargement in MEN-1 may progress to a highly aggressive ACC. Once the diagnosis of an ACC is established, the prognosis is poor, as was the case in three of four of our patients so far. ACC can therefore be one of the syndrome-related causes of death for MEN-1 patients. Newly diagnosed adrenal lesions should be followed closely. Repeat imaging studies (CT or MRI) should be performed after 3 months to avoid a dramatic clinical course, as in the two patients described above. Furthermore, it is not clear at what size the tumors should be removed. Given the fairly high prevalence of ACC in MEN-1 patients and the extremely poor prognosis of ACC, the same management as for patients with sporadic incidentalomas (removing tumors > 5 cm) does not appear to be justified. We recommend removing all adrenal tumors > 3 cm in patients with MEN-1.

Conclusions

Adrenal tumors in patients with MEN-1 are common, occurring in approximately one-fourth of patients with genetically confirmed MEN-1. Most of the tumors are nonfunctional, but the spectrum also includes adrenal Cushing syndrome and pheochromocytomas. Patients with mutations in exons 2 and 10 develop adrenal lesions significantly more often than patients with other mutations. The malignant potential of MEN-1-related adrenal neoplasia is of important clinical significance. Therefore close biochemical and radiologic follow-up is recommended. Newly diagnosed adrenal lesions should be controlled after 3 months. We recommend that all adrenal lesions larger than 3 cm in MEN-1 patients should be resected.

Résumé. Les lésions de la surrénale font partie de la gamme des syndromes des néoplasies endocrines multiples de type 1 (MEN-1). Cependant, la prévalence de la participation des surrénales, les caractéristiques et la prise en charge clinique de ces lésions de la surrénale n'ont pas encore été clairement définis. Soixante-six patients porteurs de mutations «germ-line» appartenant à un syndrome MEN-1 confirmé et un patient supplémentaire ayant des manifestations typiques d'une atteinte de trois organes ont été monitorés par un programme de dépistage comprenant une évaluation des surrénales (médiane de suivi 96 mois [12–300]). L'âge au moment du diagnostic du MEN-1 et de la tumeur de la surrénale, les caractéristiques cliniques, le génotype, le traitement et le suivi de la maladie de la surrénale ont été analysés. On a identifié une lésion de la surrénale chez 18 des 67 (26.8%) patients MEN-1; cette lésion a été diagnostiquée cinq ans plus tard que le MEN-1. La médiane du diamètre au moment du diagnostic a été de 3.0 cm, allant de 1.2 à 15 cm avec une majorité de tumeurs de 3 cm ou moins. Huit patients avaient des tumeurs bilatérales. Dix patients avaient des tumeurs bénignes non-fonctionnelles, trois avaient un syndrome de Cushing bénin et un patient avait un phéochromocytome. Quatre patients ont développé un cancer de la corticosurrénale (CAC), dont trois fonctionnels. Huit surrénalectomies ont été réalisées chez six patients. Trois patients ayant un CAC sont décédés en rapport avec leur tumeur. Les patients ayant des mutations de l'exon 2 + 10 ont développé des tumeurs de la surrénale significativement plus souvent que les patients ayant d'autres sortes de mutations ($p < 0.01$). Les tumeurs de la surrénale sont présentes souvent dans le syndrome MEN-1, mais se

développent tardivement au cours de la maladie. Les lésions sont souvent petites et non-fonctionnelles et peuvent être seulement surveillées de près. Cependant, certaines lésions ont un potentiel malin important et devraient être opérées lorsque leur taille atteint 3 cm ou plus.

Resumen. Lesiones suprarrenales forman parte del espectro del síndrome endocrino múltiple de las neoplasias tipo 1 (MEN-1). Sin embargo, se desconoce la frecuencia de la afectación de las glándulas suprarrenales, sus características clínicas y su tratamiento. 66 pacientes con MEN-1, con mutación confirmada en la línea germinal, y un paciente adicional con manifestaciones típicas en tres sistemas orgánicos, fueron monitorizados, dentro de un programa de cribado, con objeto de valorar la implicación de las suprarrenales (seguimiento medio superior a 96 meses [12–300]). Se analizaron: la edad del paciente en el momento del diagnóstico del síndrome del MEN-1 y de las neoplasias suprarrenales, características clínicas, genotipo, tratamiento y seguimiento de las lesiones suprarrenales. En 18 de los 67 pacientes, aparecieron 5 años más tarde de haber sido diagnosticados de MEN-1, lesiones suprarrenales. El diámetro medio del tumor al efectuarse el diagnóstico fue de 3.0 cm con un rango entre 1.2 y 15 cm, aunque la mayoría de las neoplasias tenían un diámetro ≤ 3 cm. En 8 pacientes se constataron tumores bilaterales. En 10 pacientes los tumores no eran funcionantes (incidentalomas), tres cursaron con un síndrome benigno de Cushing y uno presentó un feocromocitoma. 5 pacientes desarrollaron carcinomas adrenocorticales (ACC) de los que 3 eran funcionantes. Se realizaron 8 suprarrenalectomías en 6 pacientes. 3 enfermos murieron como consecuencia del ACC. Los pacientes con mutaciones en el exon 2 + 10 desarrollaron tumores suprarrenales con mucha más frecuencia que pacientes con otras mutaciones ($p < 0.1$). En el MEN-1 la existencia de tumores de las suprarrenales es frecuente, pero se manifiestan tardíamente en el curso de la enfermedad. Las neoplasias suelen ser pequeñas y afuncionantes por lo que sólo requieren una vigilancia constante. Sin embargo, algunas lesiones son potencialmente malignas y de ahí, que esté indicado el tratamiento quirúrgico de todos aquellos tumores cuyo tamaño sea ≥ 3 cm.

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