Lacrimal gland changes in sarcoidosis according to the results of spatial digital ultrasonography

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The article discusses clinical appearance of the lacrimal gland in sarcoidosis. For the first time digital ultrasonography was used to study changes in orbital tissues in 33 patients (66 orbits) with verified systemic sarcoidosis. The varieties of lacrimal gland structural changes have been investigated. As a result, pseudoedematous and combined ultrasonographic variants have been specified. Further analysis allowed identifying a number of local ultrasonographic features. The results obtained are useful for lacrimal gland assessment in patients with sarcoidosis.

Key words: lacrimal gland, sarcoidosis, ultrasonography

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Lacrimal gland (LG) involvement in the form of malfunction is found in 15-28% of patients with biopsy-confirmed sarcoidosis. According to some authors, the number of patients with «asymptomatic» LG involvement is considerably larger [11, 13]. Thus, in a retrospective study carried out by A. Karma [12], lacrimal gland ^{67}Ga uptake on orbital scintigraphy was present in 88% of patients with sarcoidosis.

A lacrimal gland can be assessed in vivo by invasive or noninvasive technique. The former implies cytological and morphological examinations of biopsy material, contrast arterio- and venography, as well as orbital ^{67}Ga scintigraphy [13].

Nonivasive clinical and functional methods include: a) visual examination; b) evaluation of LG secretion; c) evaluation of LG size and structure by means of computed tomography and magnetic resonance imaging of the orbit; d) ultrasound examination [1—10].

The objective of the present study was to analyze the results of in vivo assessment of lacrimal glands in patients with verified sarcoidosis.

Material and methods

The study is based on clinical and functional investigation of 33 patients (66 orbits) with verified sarcoidosis, who underwent outpatient or inpatient examinations at the Research Institute of Eye Diseases of the Russian Academy of Medical Sciences during 2009-2012. The age of participants ranged from 23 to 65 and averaged 45.1 years. Women prevailed in numbers (66%), while men constituted only 34%. In all patients systemic sarcoidosis was verified according to modern diagnostic criteria. Physical, laboratory, and instrumental examinations including transbronchial lymph node or lung biopsy, videotracheoscopy, and mediastinoscopy were performed in Moscow specialized medical facilities. A total of 66 lacrimal glands with ultrasonographic changes of various degrees were assessed.

The following methods were used to obtain more specific information on clinical state of the glands: 1) functional assessment with Schirmer's and Jones tests; 2) Norn test; 3) diagnostic tests with rose bengal and fluorescein; 4) conjunctival impression cytology; 5) immunology and biochemistry blood tests; 6) examination of lacrimal gland biopsy material (when indicated); 7) bilateral magnetic resonance imaging of the orbit (when indicated).

Assessment of LG structure and position was done with VOLUSON-730 Pro ("Kretz") and VOLUSON E8 digital ultrasound diagnostic systems after informed consents had been obtained and safety requirements met [1, 3, 5, 8].The linear SP 10-16 (10-16 MHz) and volume RSP 5-12 (5-12 MHz) transducers were used.

The ultrasonic analysis technique and the most common changes in ultrasonographic morphology of lacrimal glands have been already described in previous articles [1, 5, 7-9]. In order to determine which pathological features are characteristic of sarcoidosis a comparative analysis was performed with a group of 80 healthy controls aged 35 to 45 years.

The assessment scheme, applied to patients with verified sarcoidosis ,consisted of qualitative and quantitative analysis of LG intravital morphology and evaluation of its local changes. Macro- and microtexture of two- and three-dimensional virtual images as well as tissue ultrasonographic histograms were analyzed. A standard ultrasonographic slice of an LG was usually horizontal or oblique (directed upward and laterally). Initial assessment of an image consisted in measuring longitudinal (depthwise) and transversal (edgewise) dimentions of the gland. A comparison was drawn between subgroups dif-

fering by prevalent parameters and texture. The standard dimensions and their maximum deviation from the average measurements of a normal LG were analyzed.

Results and discussion

In a previous article [8] we presented the results of a study on the variety of LG changes, based on digital ultrasonography. The main variants were then designated as *atrophic*, *hypertrophic* and *combined*. The changes in spatial ultrasonographic images of patients with sarcoidosis can be referred to as combined pathological manifestations.

In order to study ultrasonographic presentation of altered lacrimal glands a number of their dimensions and structural features were comparatively analyzed (**see the table**). Bilateral LG changes (in linear dimensions, volume, and ultrasonographic texture of the tissue) were found in all 33 patients with sarcoidosis. Spatial image analysis revealed that the changes could be divided into two forms which we named *pseudoedematous* and *combined*.

Ultrasonographic signs of pseudoedematous changes in lacrimal glands were found in 11 patients (22 orbits). Most patients from this subgroup presented neither complaints, nor evident symptoms of LG involvement. However, careful history and thorough examination revealed moderate epiphora or dry eye symptoms.

Ultrasonographic signs of LG involvement in sarcoidosis

Ultrasonographic features	Number of orbits	
	Norm	Sarcoidosis
Size and volume:		
unchanged	160	18
increased	0	48
decreased	0	0
Contour:		
clear and even	0	0
clear but uneven	142	62
unclear and uneven	18	4
Capsule:		
can be visualized	102	27
can not be visualized	58	39
Mobility:		
detected	141	18
not detected	19	48
Echogenicity:		
hypoechoic	160	0
hyperechoic	0	0
combined	0	66
Echo structure:		
homogenous	32	0
heterogenous	28	66
lobular	100	0
Vascular pattern:		
unchanged	160	18
dense	0	30
rarefied	0	18
Total of orbits	160	66
Total of patients	80	33

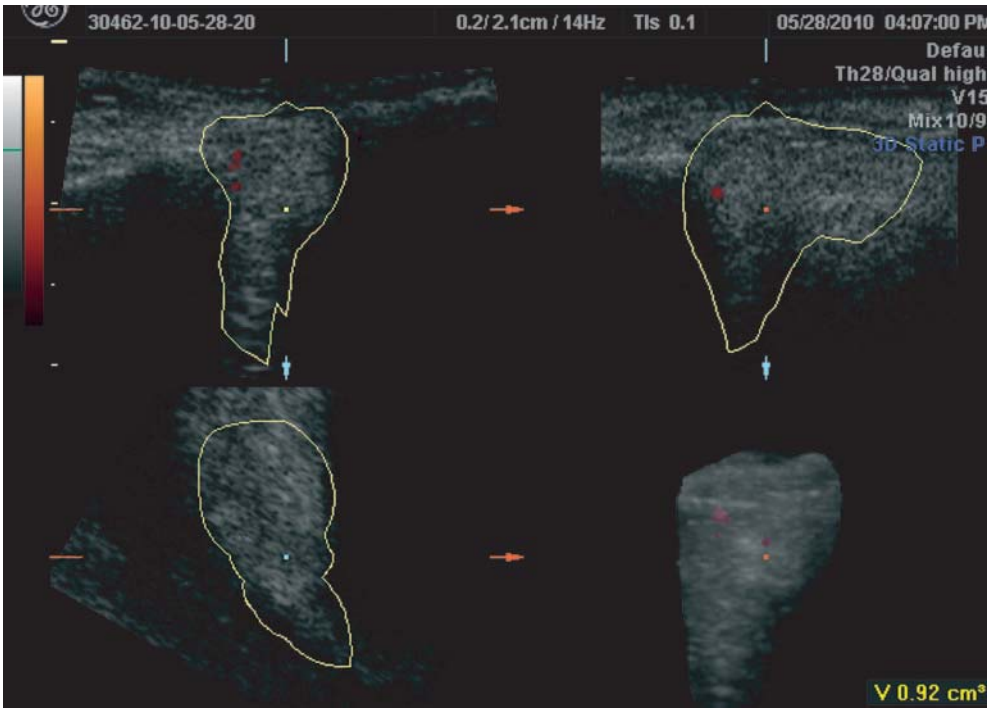


Fig. 1. **Multiplanar 3D ultrasonic analysis of a lacrimal gland in sarcoidosis. Pseudoedematous form of changes.**

Spatial ultrasonographic structure of lacrimal glands in this subgroup showed certain specific changes. Their standard length, width and height images in almost all cases were at the upper limit of normal or just beyond it. Gland slices were almost normally shaped, though a little stretched out and enlarged. Slice outlines, which corresponded to the gland capsule, were clearly visible. Texture alteration within the slice towards hypoechoic heterogeneous granular structure was also present in all cases.

Ultrasonographic slices of lacrimal glands contained a lot of small irregularly shaped granular increments which were mildly hyperechoic or echo-free, unlike the group of healthy controls, of which acoustic transparency (a special homogenous form of tissue echogenicity) was characteristic. The findings indicated homogenous consolidation and structural changes in the glands. That is where the subgroup with mentioned distinctive features in common got its name from.

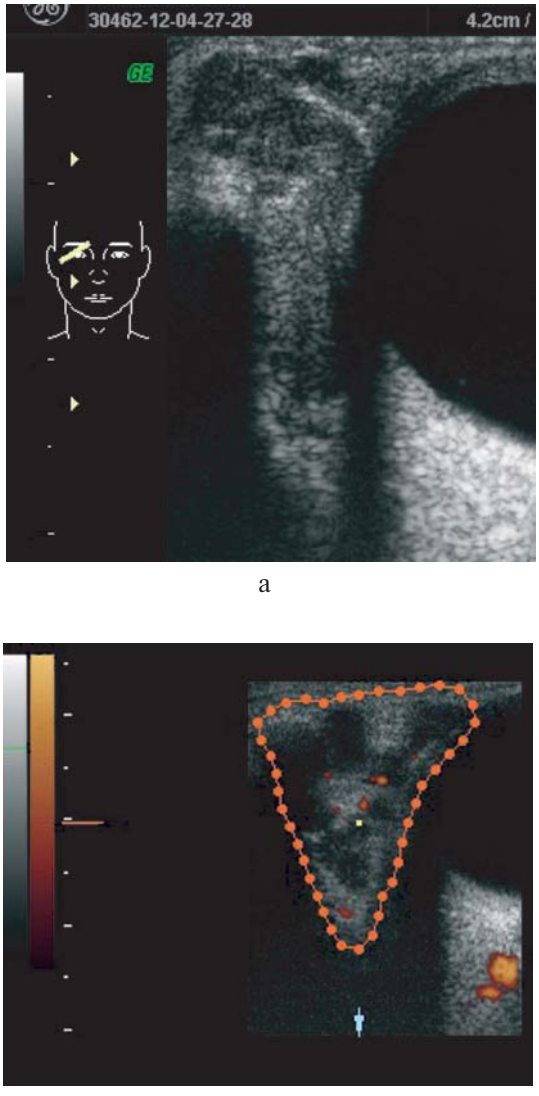
Thus, in two-dimensional images the normal lobular hypoechoic structure of lacrimal glands was distorted. The glands had the appearance of confluent heterogeneous areas with diffuse granular texture. In contrast to healthy participants, the ultrasonographic structure of lacrimal glands in this subgroup was no longer hypoechoic and airy, but blurred and fine-grained. Small rounded zones of rarefaction could be seen in the central part of LG slices. These zones appeared as irregularly shaped and fine-grained dark spots with fuzzy outlines.

In three-dimensional mode the ultrasonographic structure of the tissue in most cases was also moderately hypoechoic, heterogeneous and fine-grained. The spatial images were regularly heterogeneous throughout the whole volume. The texture looked not quite clear, and the lobules were poorly visible (**Fig. 1**).

In this subgroup large arteries and veins could only be seen deep in the tissue as single oblong color spots at the hilus projection, i.e. between the palpebral and orbital lobes of the gland. First-order vascular color maps could be easily obtained longwise. The values of lacrimal artery flow parameters were generally lower than those of healthy participants. In some cases, lacrimal artery and vein color mapping was impeded. In 6 patients (12 glands) the lacrimal artery color map could not be obtained at all.

Longitudinal and transverse dimensions of the glands in horizontal and horizontal-oblique planes ranged from 0.7 cm to 1.52 cm and from 0.3 cm to 0.6 cm, correspondingly.

Ultrasonographic density of normal lacrimal glands was 56-73 arbitrary units, while that of LGs in the first

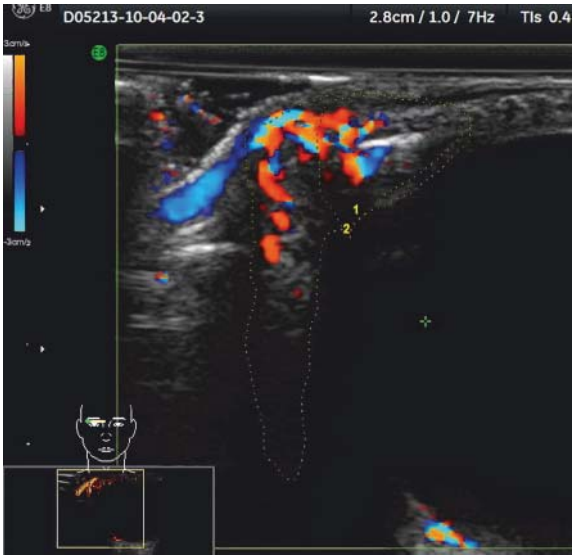


a

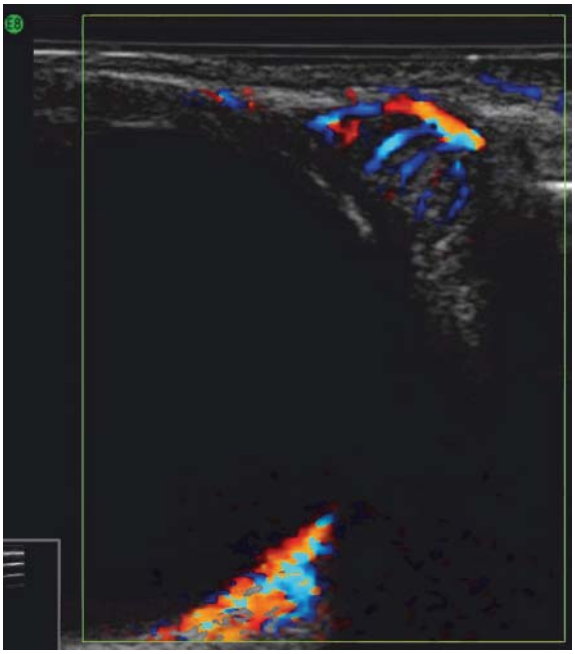
b

Fig. 2. **Rarefaction zones of ultrasonographic images of lacrimal glands resembling human (a) or cat (b) footprints.**

Fig. 3. **A 3D grey-scale image of an altered lacrimal gland. Multiple confluent irregularly shaped dark-colored lacunes are present.**



a



b

Fig. 4. **A combined ultrasound examination of the right (a) and left (b) lacrimal glands. Local accentuation of vascular pattern around a rarefaction zone in the palpebral lobe on color mapping (red for arterial, blue for venous blood flow). Significant intensification of venous blood flow.**

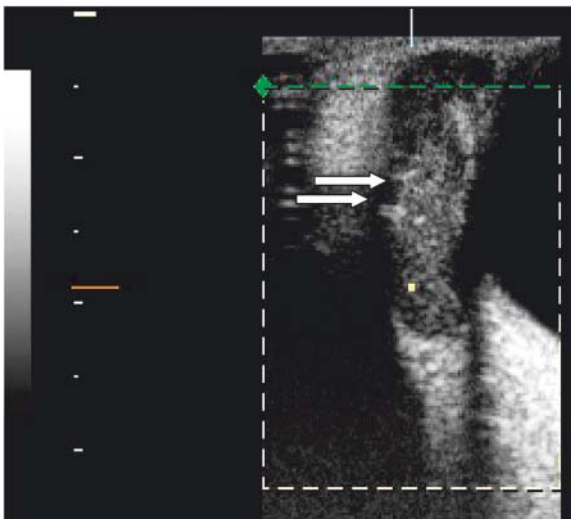


Fig. 5. **Ultrasonographic image of a lacrimal gland with combined structural changes. Arrows indicate isolated horizontal binary hyperechoic tubular structures. Signs of arteritis.**

subgroup of patients with sarcoidosis was 86—124 arbitrary units.

LG volume among healthy participants varied from 0.66 cm^3 to 0.87 cm^3 and averaged 0.72±0,15 cm^3. In the first subgroup the average LG volume was 1,2±0,15 cm^3.

Ultrasonographic sings of combined changes in lacrimal glands. In this subgroup, LG involvement was also bilateral and symmetrical. In standard projection the size of the glands proved to be increased. The average longitudinal (depthwise) dimension was 2.31±0.22 cm and transversal one (edgewise) — 1.06±0.17 cm.

Pathological ultrasonographic changes in some cases were very significant being associated with considerable functional impairment of the gland, its structure and shape alteration. LG volume averaged 4.02±0.48 cm^3, which was almost five times as much as in the group of healthy participants. Ultrasonographic structure of the glands was combined, consisting mostly of two elements.

In spatial images the glands appeared enlarged, heterogenous, stretched out and deformed, if compared to healthy participants. Gland slices typically were clearly outlined and contained large confluent round or irregularly rounded hypoechoic zones of rarefaction. Although in gray-scale images the texture of these zones was mildly granular, it still could not be called acoustically transparent, but rather black, dull and "greasy" with clear contours. In the standard projection the acoustically dense, hyperechoic component could be seen not only at the periphery of the slice, but also between the rarefaction zones. In some cases interlobular hyperechoic cords of different length and thickness were noted. The images generally resembled cat or human footprints (**Fig. 2**) due to dark shell-shaped irregularly rounded "imprints" within the gland slices.

The wider part of 2D ultrasonographic slices of the lacrimal gland pointed to the upper lateral orbital margin, while the other part was closer to the orbital apex. In longitudinal projection, gland slices were parallel to the outer contour of the eye ball and went far beyond its posterior pole. Analysis of combined 3D virtual models of

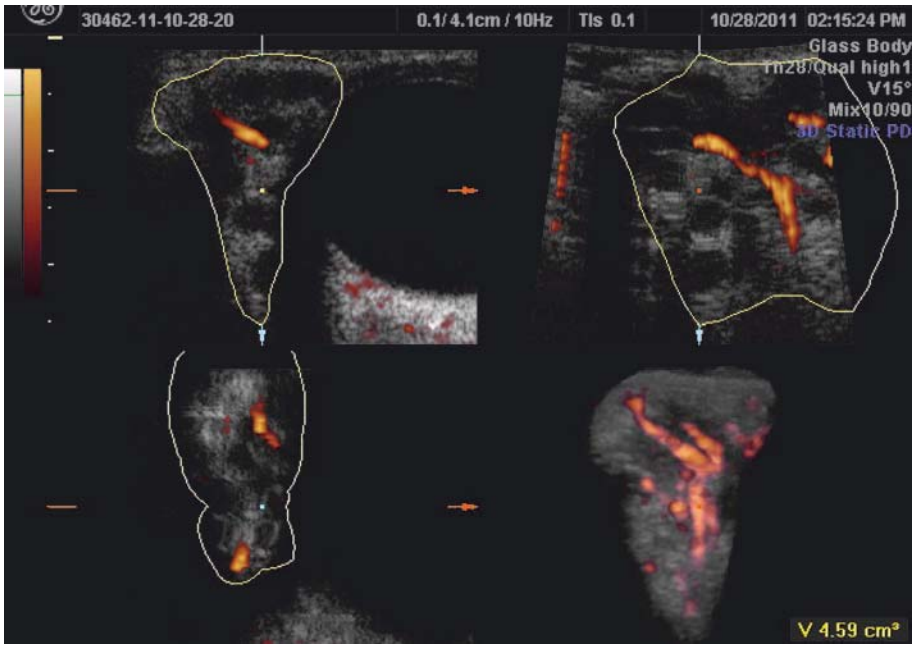


Fig. 6. **Multiplanar spatial ultrasonic analysis of a combined 3D reconstruction of an altered lacrimal gland (explanation in the text).**

the glands by means of rotation helped to visualize spatial structure deformities within the rarefaction zones **(Fig. 3)**. The latter appeared as multiple confluent irregularly rounded dark-colored lacunes in the gland tissue.

Lobular structure of the glands was distorted both in plane and spatial images. According to color mapping, vascular pattern of the glands was accentuated but complied with normal distribution of the vessels. In most cases the venous component was enhanced (**Fig. 4**). In combined spatial images of 10 patients, small in number (up to three) binary horizontal hyperechoic tubular structures were found. These were designated as "sheaths" and are likely to be an ultrasonographic sign of arteritis, i.e. granulomatous wall inflammation in vessels of II and III order (**Fig. 5**).

Systolic parameters of lacrimal artery in Doppler ultrasonography proved to be higher than those in healthy participants. Spatial vascular pattern of the glands could be called "reactive" with II and III order branches of *a.* and *v. lacrimalis* seen over the whole gland slice. Within the zones of rarefaction there was no local hypervascularization that could be interpreted as neovascularization (**Fig. 6**). However, around these zones, vascular density was higher than usual and approximated the vascular reaction in acute dacryoadenitis.

In five patients from this subgroup morphological examination of biopsy material was performed. The results confirmed sarcoidosis-induced changes.

Conclusion

Lacrimal gland involvement in sarcoidosis should be suspected in patients with swelling of the upper eyelid lateral segment. Gland changes can be discovered during a physical examination by means of transpalpebral or transconjunctival palpation. Significant enlargement of the gland sometimes causes ptosis, hyperemia and eyelid edema. These can be signs of sarcoidosis-induced dacryoadenitis. In dubious cases a diagnosis can be confirmed by lacrimal gland biopsy. According to literary sources, biopsy is considered necessary if the gland is hard and well palpated and/or if it shows ^{67}Ga uptake on scintigraphy [13].

Modern diagnostic ultrasound technologies also provide the opportunity for intravital assessment of the lacrimal gland and evaluation of possible changes in its condition. They allow to measure dimensions of the gland, determine its shape and structure, as well as topographic relationship with other orbital structures. Different systemic diseases, including sarcoidosis, can affect the gland both directly and indirectly, causing structural changes in its tissue or a functional reaction, characteristic for organs of immune surveillance. Timely discovering of these changes provides additional diagnostic information on orbital manifestations of sarcoidosis.

Principles of diagnostics of lacrimal gland involvement in sarcoidosis. As a result of the study, main variants of

ultrasonographic structural changes of lacrimal glands in sarcoidosis were defined and designated as pseudoedematous and combined forms. A special algorithm of ultrasound examination for such patients was developed. It consists in step-by-step evaluation of spatial and structural ultrasonographic parameters. Analysis of the obtained data enabled to identify the following characteristic local changes:

1) changes of the gland in shape and size (longitudinal and transverse) not associated with significant distortion of its structure, which are diagnosed by analyzing the outline of an ultrasonographic slice of the gland or by reconstructing its virtual volume;

2) changes of the gland in size and structure, which are diagnosed by texture analysis of longitudinal ultrasonographic slice and so called acoustical transparency analysis, as well as virtual reconstruction of gland volume;

3) alteration of lacrimal gland surface (in contact with surrounding tissues), which is diagnosed by analyzing the surface texture of 3D gland reconstruction;

4) changes in gland vascular pattern (both increase and decrease of vascular density) according to color and power Doppler mapping;

5) adverse effects on vascular walls of lacrimal gland vessels seen in gray-scale images.

The comparison of ultrasonographic appearance of lacrimal glands in sarcoidosis with results of morphological examination of biopsy material has been performed in only five cases. That is why we cannot either prove specificity of the detected changes or attribute them to a certain stage of the disease. At the same time LG structure was found to be altered in all cases of sarcoidosis regardless of local manifestations and process severity. The findings can be partly used in lacrimal gland assessment in patients with sarcoidosis.

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