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MODERN ASPECTS OF THE TREATMENT OF PATIENTS WITH AUTOIMMUNE THYROIDITIS

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Abstract

The relevance of the problem is due to the continuous increase in morbidity and the lack of effectiveness of existing treatment methods. The aim of the study is to improve the treatment results of patients with autoimmune thyroiditis by introducing modern laser technology. The study was conducted retrospectively from 2008 to 2021 and is based on data from the examination and treatment of 481 patients with autoimmune thyroiditis. The patients were divided into groups according to the applied treatment methods: the first group - 129 (29,19%) patients, the second group - 106 (23,98%) patients, and the third group - 207 (46,83%) patients. The concentrations of thyroid hormones, pituitary gland and antibodies to thyroid tissues in the blood serum of patients before and after treatment were studied and compared. Long-term treatment results were studied in 340 (70,7%) patients ($t=8,8$, $p \leq 0,001$). Photodynamic therapy, in combination with sessions of intravenous laser blood irradiation with low-intensity laser radiation, contributed to the normalization of thyroid hormone levels (TSH, FT4 and FT3) of the thyroid gland on the 15th day of treatment. Combining conservative treatment of patients with autoimmune thyroiditis with photodynamic therapy allows to obtain good and satisfactory results in 77,5% of cases, which gives reason to recommend photodynamic therapy in combination with sessions of intravenous laser blood irradiation with low-intensity laser radiation as an effective way to complement traditional conservative treatment.

Аутоиммунды тиреоидитке шалдыққан науқастарды емдеудің заманауи аспектілері

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Тұжырым

Мәселенің өзектілігі осы аурудың үздіксіз өсу деңгейіне және қолданыстағы емдеу әдістерінің тиімсіздігіне негізделген. Зерттеудің мақсаты – заманауи лазерлік технологияны енгізу арқылы аутоиммунды тиреоидитке шалдыққан науқастарды емдеу нәтижелерін жақсарту. Зерттеу 2008-2021 ж. аралығында ретроспективті түрде жүргізілді және аутоиммунды тиреоидитке шалдыққан 481 науқасқа тиесілі қарап-тексеру және емдеу деректерін негіз ретінде алған. Науқастарға қолданылған емдеу әдістерін ескере отырып, олар мынадай топтарға бөлінді: бірінші топ – 129 (29,19%) науқас, екінші топ – 106 (23,98%) науқас, үшінші топ – 207 (46,83%) науқас. Науқастардың емделуге дейінгі және одан кейінгі қан сарысуындағы қалқанша безінің гормондарының, гипофиздің және қалқанша безінің тіндеріне антиденелердің концентрациясының көрсеткіштері зерттелді және салыстырылды. Емдеудің ұзақ мерзімді нәтижелері 340 (70,7%) науқас арқылы зерттелді ($t=8,8$, $p \leq 0,001$). Фотодинамикалық терапия төмен қарқынды лазерлік сәулеленудің көктамыршілік лазерлік сәулелену сеанстары арқылы жанама емдеудің 15-күнінде қалқанша безі гормондарының (TSH, svt4 және svt3) деңгейін қалыпқа келтіруге ықпал етті. Аутоиммунды тиреоидитке шалдыққан науқастарды консервативті емдеуді фотодинамикалық терапиямен күшейту бақылаулардың 77,5%-ында жақсы және қанағаттанарлық нәтижелерге қол жеткізуге мүмкіндік береді, бұл дәстүрлі консервативті емдеуді толықтырудың тиімді әдісі ретінде төмен қарқынды лазерлік сәулеленуді, көктамыр ішіне лазерлік сәулелену сеанстарымен бірге фотодинамикалық терапияны ұсынуға негіз береді.

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Современные аспекты лечения больных аутоиммунным тиреоидитом

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Аннотация

Актуальность проблемы обусловлена непрерывным ростом заболеваемости и недостаточной эффективностью существующих методов лечения. Целью исследования является улучшение результатов лечения больных аутоиммунным тиреоидитом путем внедрения современной лазерной технологии. Исследование проводилось ретроспективно в период с 2008 по 2021 год и основана на данных обследования и лечения 481 больного аутоиммунным тиреоидитом. Больные разделены на группы с учетом примененных методов лечения: первая группа 129 (29,19%) больных, вторая группа 106 (23,98%) больных и третья группа 207 (46,83%) больных. Исследованы и сравнены показатели концентрации гормонов щитовидной железы, гипофиза и антител к тканям щитовидной железы в сыворотке крови пациентов до и после лечения. Отдаленные результаты лечения изучены у 340 (70,7%) пациентов ($t=8,8$, $p\leq 0,001$). Фотодинамическая терапия в сочетании с сеансами внутривенного лазерного облучения крови низкоинтенсивным лазерным излучением способствовала нормализации показателей уровней гормонов (ТТГ, св. Т4 и св. Т3) щитовидной железы на 15 день лечения. Потенцирование консервативного лечения больных аутоиммунным тиреоидитом фотодинамической терапией позволяет получить хорошие и удовлетворительные результаты в 77,5% наблюдений, что даёт основание рекомендовать фотодинамической терапии в сочетании с сеансами внутривенного лазерного облучения крови низкоинтенсивным лазерным излучением как эффективный способ, дополняющий традиционное консервативное лечение.

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Introduction

According to the literature data, the frequency of autoimmune thyroiditis (AIT) is up to 35% among all thyroid diseases [5]. The issue of choosing a method of treatment for patients with autoimmune thyroiditis is still far from a final solution. Despite reasonable indications for surgical treatment of nodular forms of AIT, the choice of treatment for patients with a diffuse form of the disease remains open. The diffuse form of AIT occurs in approximately 40-60% of patients [6,16]. The clinical picture of the disease is determined by the severity and prevalence of pathological changes in the thyroid gland [7].

The relevance of the problem lies not only in the timely and accurate diagnosis of the disease but also in a clear prognosis during the course of the disease, which is very important in choosing an adequate method for treating autoimmune thyroiditis for each patient. Conducting long-term courses of drug therapy have a temporary positive effect, but after stopping therapy, 20%-45% of patients experience a relapse of AIT since drugs help relieve symptoms but do not solve the true problem-eliminating autoimmune inflammation [6,11]. Long-term use of corticosteroids, which have immunosuppressive, anti-allergic, and anti-inflammatory effects, can lead to the development of drug-induced cushingoid, and these drugs do not prevent, but on the contrary, can aggravate hypothyroidism [14,15].

Patients with autoimmune thyroiditis turn to various specialists, who, for a number of objective and subjective reasons, can't establish an accurate diagnosis and provide effective medical care. Even with a verified diagnosis of AIT, long-term courses of conservative therapy often bring only a temporary effect. This situation cannot satisfy specialists who provide care to such patients and requires the development of new, more effective treatment methods that can optimize the treatment results of patients with AIT and reduce disability rates and treatment costs [1,10].

In recent decades, in search of new, more effective means and methods for treating AIT, a number of researchers have proposed the use of infrared laser therapy in the treatment of AIT [8,13]. The authors note that AIT is the main cause of hypothyroidism and leads to the development of pathological changes in the reproductive system of women in the form of menstrual disorders, infertility, and increased morbidity during pregnancy and gestation.

Based on the discovered immunomodulatory and anti-inflammatory effects of photodynamic therapy (PDT), in recent years, laser PDT has been successfully introduced into clinical practice in the treatment of benign and malignant skin tumors of various localizations, psoriasis, and inflammatory processes of autoimmune genesis [3,12]. It should be

noted that the action mechanism of photodynamic therapy is the formation of reactive oxygen species that cause the death of activated macrophages (without damaging healthy tissues) after the selective accumulation of the photosensitizer in inflammatory cells and microflora and its activation by laser radiation. Laser photodynamic therapy has an anti-inflammatory, antihistamine, desensitizing, suppressing free radical oxidation and stimulating reparative processes action, as well as an immunocorrective effect due to a decrease in the level of antibodies to thyroperoxidase [2,4].

Intravenous laser blood irradiation (ILBI), in turn, has a positive multifactorial effect on the function of organs and systems, the most important of which are: activation of blood microcirculation, activation of the oxygen transport function of blood and tissue respiration, restoration of the balance of the coagulation and anticoagulation systems, stabilization of the ratio of the T-helper subpopulation /T-suppressors, anti-inflammatory, immunocorrective, stimulating reparative processes, and increasing the level of tissue nutrition action [8,9]. These positive effects make it possible to approve the combined use of laser PDT and intravenous laser blood irradiation (ILBI) in the treatment of various forms of autoimmune thyroiditis.

The aim of the study - is to improve the treatment results of patients with autoimmune thyroiditis by introducing modern laser technology.

Materials and methods

The paper analyzes the examination and treatment results of patients with autoimmune thyroiditis (AIT) hospitalized at the clinical base of the Scientific center of surgery named after academician M.A. Topchubashov from 2008 to 2021. We examined 481 patients aged 27 to 73 years. There were 438 women (91,1%) and 43 men (8,9%). Out of 481 patients treated in the clinic, the results of monitoring 442 (91,9%) patients who received various types of treatment were analyzed. 39 (12,50%) patients who had signs of atypia and malignancy of thyroid cells during puncture biopsy were referred to oncologists for further examination and treatment. Long-term treatment results were studied in 340 (70,7%) patients ($t=8,8, p<0,001$).

The patients were divided into three groups based on the treatment methods used. The first group included 129 (29,2%) patients who received a course of conservative therapy in combination with sessions of intravenous laser blood irradiation with low-intensity laser radiation (ILBI-LILR). The "Solaris" apparatus (Russia) was used for intravenous laser blood irradiation. 103 (79,8%) patients were followed up during the follow-up period from 1 to 5 years. For replacement therapy, levothyroxine preparations were prescribed approximately at the rate of 1,7 µg/kg/day of the patient's body weight.

The second group included 106 (24,0%) patients who were treated with laser photodynamic therapy (PDT) and ILBI-LILR sessions. 80 (75,5%) out of

106 patients in this group were followed up for 3-5 years inclusive. For laser photodynamic therapy, the phototherapeutic apparatus AFS "Harmony" (Russia) was used. The third group consisted of 207 (46,8%) patients who underwent surgery for a complicated form of AIT. In the postoperative period, 96 patients of this group received 7-8 courses of intravenous laser blood irradiation with low-intensity laser radiation (ILBI-LILR). Among the patients of the third group, we tracked the long-term results of 157 (77,7%) of 207 patients for 3-5 years after surgery.

We analyzed complaints, clinical and anamnestic data, and results of instrumental, laboratory, and morphological studies. The determination of thyroid status and the level of autoantibodies to antigenic structures of the thyroid gland tissue was carried out by measuring the concentration of thyroid hormones (FT3, FT4), pituitary gland (TSH), and antibodies to thyroid tissues Anti-TG, Anti-TPO in serum of patients by enzyme immunoassay.

All calculations were carried out on the EXCEL-2016 spreadsheet. Statistical analysis was performed using the IBM SPSS Statistic version 23 software package (SPSS: An IBM Company, USA). Pearson's χ^2 test was used to test the statistical significance of differences in the concentrations of thyroid hormones, pituitary gland, and antibodies to thyroid tissues in the blood serum of patients before and after treatment. In each group of patients, the average values of the analyzed clinical parameters, their mean error ($\pm m$), 95% confidence interval, and the significance of intergroup differences according to Pearson's χ^2 , Mann-Whitney U, Student's t test, or Fisher's exact test (if at least in one of the cells of the contingency table, the number of observations was less than five). Differences were considered statistically significant at $p<0,050$.

Results and discussion

All 442 patients were divided into three age groups: the first group (people of young age 16-35 years old) - 52 (11,8%) patients, the average age of which was 29,0 [16,0-35,0]; the second group (people of average age 36-59 years) - 251 (56,8%) patients, their average age was 54,0 [36,0-59,0]; the third group (elderly people aged 60-74 years) - 139 (31,4%) people, the average age of the representatives of this group was 69,0 [60,0-74,0] (I and III age groups were statistically different from II group ($p<0,0001$)). The data obtained indicate that almost 2/3 of patients are people of working age (68,6%).

Table 1. presents the methods used to treat patients of various age groups. The data allows us to note that the majority of patients who underwent surgical treatment for AIT are elderly people - 124 (59,9%) out of 207 patients. Sessions of photodynamic therapy were received in approximately equal parts among young and average aged patients, as well as elderly patients, in 54 (50,9%) and 52 (49,1%) patients, respectively. A course of conservative therapy was carried out in more cases in elderly patients - 70 (54,3%) out of 129 people (Table 1).

Treatment method		Young and average age patients 16-59 y.	Elderly patients 60-74 y.	Total
Conservative therapy + ILBI-LILR		59 (45,7%)	70 (54,3%)	129 (29,2%)
Photodynamic therapy +ILBI-LILR		54 (50,9%)↓*	52 (49,1%)↓*	106 (24,0%)
Surgical treatment	Subgroup A+ ILBI-LILR	33 (34,4%)↑*	63 (65,6%)↑*	96 (21,7%)
	Subgroup B	50 (45,1%)	61 (54,9%)	111 (25,1%)
Summary		196 (44,3%)→*	246 ←*(55,7%)	442 (100%)

Table 1. Treatment methods of patients with AIT in different age groups

Note: * statistically significant differences ($t \geq 2,0$, $p \leq 0,05$)

It should be noted that there was a rather high frequency of comorbidities, among which the most frequently detected were: hypertension in 250 (51,9%) and coronary heart disease in 226 (47,0%) patients. It is noteworthy that every third patient is diagnosed with chronic diseases of the gastrointestinal tract, obesity, and diabetes.

To assess the effectiveness of PDT in combination with ILBI-LILR, we studied the parameters of thyroid hormones. The study was conducted on patients of the first (50 (38,8%) out of 129) and second (40 (37,7%) out of 106) groups. The concentrations of thyroid hormones (FT₃; FT₄), pituitary gland (TSH), and antibodies to thyroid tissues (Anti-TPO) in the blood serum of patients before and then on the 15th day after treatment were studied and compared. When analyzing the data, it was revealed that in patients of the second group, the indicators of Anti-TPO, TSH, FT₄ and FT₃ clearly improved and approached normal figures, which indicates the absence of signs of

hypothyroidism in patients of this group.

In patients of the first group, we noted some changes, primarily related to a decrease in the level of TSH (before treatment: $9,99 \pm 1,34$ μ IU/ml; on day 15 after treatment: $3,13 \pm 0,82$ μ IU/ml ($t=6,9$, $p \leq 0,001$)) by 3,2 times, an increase of 1,58 times in the concentration of FT₃ (before treatment: $3,10 \pm 0,66$ pmol/l; on day 15 after treatment: $4,89 \pm 0,86$ pmol/l ($t=4,3$, $p \leq 0,005$)), and a decrease in Anti-TPO values by 4,94 times (before treatment: $326,28 \pm 46,89$ IU/ml; on day 15 after treatment: $65,95 \pm 9,31$ IU/ml ($t=5,4$, $p \leq 0,001$)).

Statistical differences in the second group between the indicators before and on day 15 after treatment were, respectively, $t=8,39$, $p \leq 0,001$; $t=4,78$, $p \leq 0,001$; $t=3,51$, $p \leq 0,01$ and $t=1,42$, $p \geq 0,05$. Statistical differences in the first group between the indicators before and on day 15 after treatment were $t=5,40$, $p \leq 0,001$; $t=4,37$, $p \leq 0,001$; $t=5,11$, $p \leq 0,001$ and $t=1,66$, $p \geq 0,05$ (Table 2).

Averages	Before treatment (avg/min/max)		15 days after treatment	
	First group (n=50)	Second group (n=40)	First group (n=50)	Second group (n=40)
TSH μ IU/ml norm 0,27-4,2	$9,99 \pm 1,34$ [6,04-11,85]	$6,54 \pm 0,47$ [5,65 - 7,54]	$3,13 \pm 0,82$ [1,49-4,77]	$3,00 \pm 0,21$ [2,58-3,42]
FT ₄ pmol/l norm 120-22,0	$6,69 \pm 1,36$ [8,98 - 4,91]	$10,20 \pm 2,05$ [12,95 - 7,63]	$16,40 \pm 1,39$ [13,62 - 19,18]	$19,15 \pm 1,52^{**}$ [16,11 - 22,19]
FT ₃ pmol/l norm 3,1-6,8	$3,10 \pm 0,66$ [4,38 - 2,07]	$2,99 \pm 1,01$ [4,53 - 1,47]	$4,89 \pm 0,86$ [3,17 - 6,61]	$5,11 \pm 1,10$ [2,91 - 7,31]
Anti-TPO <34 IU/ml	$326,28 \pm 46,89$ [248,03-399,02]	$176,80 \pm 16,29$ [147,3 - 205,0]	$65,95 \pm 9,31$ [47,33 - 84,57]	$31,57 \pm 5,75^{**}$ [20,07- 43,07]

Table 2. Indicators of hormone levels in patients with autoimmune thyroiditis before and then on the 15th day after treatment (average values)

Note: $p \leq 0,001^{**}$ statistical significance of differences between the first and second groups

15 days after treatment, the average values of Anti-TPO in the second group are within the normal range ($31,57 \pm 5,75$ IU/ml), while the average values of Anti-TPO in the first group ($65,95 \pm 9,31$ IU/ml) exceed the norm by 1,9 times ($t=3,15$, $p \leq 0,05$).

The absence of signs of hypothyroidism in patients of the second group is also confirmed by clinical observations of patients and ultrasound data on the state of the thyroid gland. In patients of the first group, conservative therapy brought a positive result in only 82 (63,6%) patients, while in 47 (36,4%) of 129 patients, signs of subclinical hypothyroidism,

as well as structural changes in the thyroid gland persisted at later dates (21 days or more). As a result, it was impossible to achieve complete rehabilitation of all 129 patients. There are statistically significant differences between the number of positive results and the number of patients who failed to achieve complete rehabilitation ($t=4,5$, $p \leq 0,001$).

The surgical method requires an individual approach in the treatment of autoimmune thyroiditis. This is primarily due to unsatisfactory long-term results of surgical interventions in this disease. In this regard, 207 (46,8%) out of 481 patients had

reasonable indications for surgical treatment. The scope of the operation varied from subtotal resection of the thyroid gland - 69 (33,3%) patients - to extremely subtotal resection of the thyroid gland - 43 (20,8%) patients - and thyroidectomy - 95 (45,9%) patients. In most cases, operations for AIT are technically difficult and often accompanied by complications, both during the operation and in the early postoperative period. According to the clinical examination of patients with autoimmune thyroiditis and their individual characteristics, the complicated course of diffuse-nodular (in 72,4% of cases) and diffuse-pseudonodular (73,3%) forms of autoimmune thyroiditis were observed. Growth and enlargement of the thyroid gland (formation of nodular or multinodular goiter), clinical hypothyroidism, the risk of developing thyroid cancer are indications for surgical treatment.

In the third group, among patients who underwent surgery, we identified two subgroups of patients. Subgroup "A" consisted of 96 (21,7%) patients for whom CO2 laser was used as an instrument during surgery. In the same group of patients, an improved surgical technique was used, which allows for surgical intervention under visual control of the areas of localization of the upper laryngeal nerve and parathyroid glands, which reduced the risk of damage to these structures during surgery. The use of the described surgical techniques allowed to reduce the number of patients with laryngeal paresis and

hypoparathyroidism by more than twice. In addition, in the early postoperative period, patients of the same group underwent sessions of intravenous laser blood irradiation with low-intensity laser radiation (ILBI-LILR) for faster recovery.

Subgroup "B" consisted of 111 (25,1%) patients for whom traditional surgical techniques and standard management of the early postoperative period were used during surgical intervention on the thyroid gland. According to the data given in tab. 3, it should be noted that the frequency of complications in subgroup "A" of patients is more than twice lower than the same indicators among patients of subgroup "B". The indicators of the average bed-day are also lower in patients of subgroup "A" by 22%.

Statistical processing of data in table 3 (Fisher's exact test), where $p < 0,093$, confirmed significant differences in morbidity and mortality in the two comparison subgroups. The data presented in Table 3 indicate that the number of patients with complications among patients of subgroup "A" (3) is three times less than the number of patients with complications (10) among patients of subgroup "B" (Fisher's exact test $p < 0,371$). The greatest number of complications was noted in the group of patients in whom the indications for surgical treatment were large goiters and recurrence of the disease that occurred in patients previously operated on for autoimmune thyroiditis (Table 3).

Table 3. Complications and mortality during surgical interventions in two subgroups of patients operated on for autoimmune thyroiditis

Sub groups	Num. patients	The nature of the complications					All patients	
		Paresis of the larynx	Hypoparathyroidism	Suppuration of the wound	Bleeding from a wound	Average bed day	With complications	Died
Subgroup A	96	2 (2,1%)	1 (1,1%)	-	-	7,4	3 (3,1%)	1 (1,1%)
Subgroup B	111	3 (2,7%)	3 (2,7%)	2 (1,8%)	2 (1,8%)	9,1	10 (9,0%)	4 (3,6%)
Summary	207 (100)	5 (2,4%)	4 (1,9%)	2 (1,0%)	2 (1,0%)	8,0	13 (6,3%)	5 (2,4%)

Long-term results were assessed as good if the patient was free from the disease and remained healthy, was in a euthyroid state, which was ensured by the normal functional activity of the thyroid gland, levothyroxine replacement therapy was not prescribed or was prescribed at a dose not exceeding 25 µg/kg/day. The result was considered satisfactory if the patient noted a significant improvement in his condition and retained his ability to work, while the functional state of the thyroid gland or thyroid residue was significantly reduced, and the euthyroid state was

achieved by prescribing replacement therapy with levothyroxine at a daily dose of 50 µg/kg/day.

The group of unsatisfactory results is represented by patients who continue to get sick, have a functionally unstable state of the thyroid system, and constantly need treatment or reoperation. The working capacity of these patients is either reduced or lost. The treatment results of 340 (70,7±2,1%) patients were studied. 75(22%) had good results, 203(60%) had satisfactory results, and 62(18%) had poor results (Table 4).

Table 4. Long-term treatment results of patients with AIT in three groups, taking into account the method of their treatment

Groups	Good	Satisfactory	Unsatisfactory	Total
I	12 ** (11,7±3,2%)	54 ** (52,4±4,9%)	37** (35,9±4,7%)	103 (30,3±2,5) 100%
II	14 ** (17,5±4,2%)	48 ** (60,0±5,5%)	18 ** (22,5±4,7%)	80 (23,5±2,3) 100%
III	49 ** (31,2±3,7%)	101** (64,3±3,8%)	7 *** (4,5±1,7%)	157 (46,2±2,7) 100%
Total	75*** (22,1±2,3%)	203 *** (59,7±2,7%)	62 *** (18,2±2,1%)	340 100%

Note: **statistically significant differences $p \leq 0,005$.
*** statistically significant differences $p \leq 0,0001$.

Thus, the number of patients with unsatisfactory treatment results was 62 (18,2±2,1%) out of 340 patients followed. The majority were patients of group I (37 (59,7%) out of 62 people) - people who received courses of conservative therapy in combination with ILBI-LILR. Patients who underwent surgery were represented the least in this group (7 (11,3%) people out of 62).

In total, the best results were achieved among operated patients (group III) and patients who underwent PDT sessions in combination with ILBI-LILR (group II). The percentages of patients with good and satisfactory treatment results in these groups were 95,5% and 77,5%, respectively. Statistical processing of the data given in table 4. confirmed a significantly higher proportion of patients with good and satisfactory treatment results in groups III and II. The value according to Pearson's χ^2 criteria for all three groups of patients was - $p < 0,001$.

The data of clinical and laboratory examination

of patients with various forms of autoimmune thyroiditis recorded favorable results for a rational approach to the diagnosis and treatment of patients with this disease. From here, we conclude that patients who underwent surgical treatment for autoimmune thyroiditis actually belong to patients with a complicated course of the disease.

Conclusions

The proposed improved method using laser technology provides better results in the treatment of patients with diffuse autoimmune thyroiditis. Possessing a pronounced local effect on the cell-tissue structure of the thyroid gland, the combined use of laser radiation can provide a favorable effect and a positive outcome in the treatment of the disease. Laser PDT in combination with ILBI-LILR sessions brought good and satisfactory results in 77,5% of cases, which gives reason to recommend it for use in patients with diffuse and atrophic forms of AIT, as well as in women with postpartum thyroiditis.

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