

CHRONIC GRANULOMATOUS DISEASE AND PERIPHERAL ULCERATIVE KERATITIS: A RARE CASE OF RECURRENT EXTERNAL OCULAR DISEASE

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SUMMARY

Clinical report: We report a case of a 29-year-old lady, with known Chronic Granulomatous Disease, who presented with an acneiform scarring facial and trunk eruption and sore red eyes. Slitlamp examination showed limbal granulomas and adjacent peripheral ulcerative keratitis.

Discussion: The authors are considering the possible causes of the keratitis. As there were no signs of blepharitis at the time of initial presentation, the keratitis was most likely mediated by the adjacent limbal granuloma, and not due to Staphylococcal hypersensitivity.

Conclusion: Although ocular involvement in CGD has been described before, this is the first article that describes limbal granulomata and peripheral ulcerative keratitis. Multidisciplinary management with longstanding oral antibiotic treatment, and topical combined antibiotic-steroid treatment were required to bring the condition under control.

RÉSUMÉ

Cas clinique: Nous rapportons le cas d'une femme de 29 ans, connue avec la Maladie Granulomateuse Chronique (MGC), qui se présentait avec une éruption acnéiforme faciale et troncale et une irritation oculaire. L'examen biomicroscopique montrait des granulomes limbiques adjacents à une kératite ulcéreuse périphérique.

Discussion: Les auteurs considèrent les causes probables de la kératite. Comme il n'y avait pas de signes de blépharite au moment de la première présentation, la kératite était probablement due aux granulomes limbiques, et non à une hypersensibilité au *Staphylococcus Aureus*.

Conclusion: Des manifestations oculaires ont été décrites dans le cadre de la MGC, mais c'est le premier cas qui décrit des granulomes associés à la kératite ulcéreuse périphérique.

Une approche multidisciplinaire à long terme, avec un traitement antibiotique oral et une préparation combinée antibiotique-corticoïde topique, a été nécessaire.

KEY WORDS

Chronic Granulomatous Disease, peripheral ulcerative keratitis, limbal granulomas, blepharitis, meibomian gland disease.

MOTS CLÉS

Maladie Granulomateuse Chronique, kératite ulcéreuse périphérique, granulomes limbiques, blépharite, méibomite.

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INTRODUCTION

CHRONIC GRANULOMATOUS DISEASE (CGD) is a rare congenital immunological disorder characterized by recurrent life-threatening infections and granuloma formation (5,9,21). In the absence of antibiotic prophylaxis, patients may develop severe infections. The liver and lungs are frequently involved.

We report a case of limbal granulomas and peripheral ulcerative keratitis in a young female patient with CGD. We are unaware of any previous report of limbal granulomas or peripheral ulcerative keratitis and could find no references by a computer search of MEDLINE using the search terms chronic granulomatous disease and the eye.

CASE REPORT

A 29-year-old female with known cutaneous chronic granulomatous disease, presented with a 1-week history of sore, red eyes.

Her medical history was of chronic granulomatous disease since early childhood, treated with Co-trimoxazole 960 mgs per day and Itracozazole 100 mgs per day. Previous investigations had confirmed a diagnosis of Variant CGD with p67phox deficiency on western blot and 15% superoxide function on neutrophil function tests. Her mother is known to be a carrier of CGD. Her brother was also affected with the disease, but had minimal cutaneous disease, controlled by Trimethoprim 200 mg bd only. Examination showed an inflammatory, acneiform facial and trunk rash. The facial involvement was in a butterfly distribution (Figure 1). Facial swabs revealed *Ochrobactrum anthropi*, *Staphylococcus aureus* and beta-haemolytic *Streptococcus*. A facial diagnostic biopsy was performed to exclude the possible differential diagnosis of cutaneous lupus erythematosus (8,11). The facial skin histology showed granulomatous dermatitis, with no features of cutaneous lupus and consistent with the diagnosis of CGD. Direct immunofluorescence of perilesional skin was negative. Serum auto-antibody screen was also negative.

Ocular examination demonstrated a best-corrected visual acuity of 20/25 in both eyes. The right eye was inflamed inferiorly. Slitlamp examination revealed two elevated inferior lim-

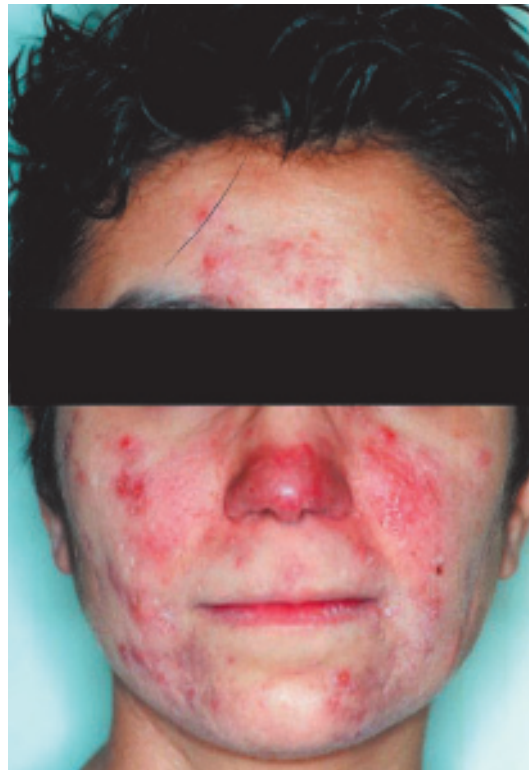


Fig 1. Acneiform facial rash.

bal granulomas in the right eye and deeply excavating peripheral ulcerative keratitis adjacent to the granulomas (Figure 2-3). The ulceration excavated deeply to an estimated 80% depth of the peripheral cornea. The peripheral edge of the ulcer revealed a greyish inflammatory infiltrate. The anterior chambers were quiet, and intraocular pressures were within normal limits. The ocular media were clear and fundus examination was unremarkable. Treatment was initiated with guttae Ofloxacin 0.3% six times per day and guttae Prednisolone 0.5% five times per day.

The ulcerations on the peripheral cornea epithelialized and healed over three months, leaving thinned, grey, vascularized peripheral scars. The drops were tapered over this period according to inflammatory signs.

Subsequently four recurrences developed over the following three years, once in the left eye and thrice in the right eye. All the recurrences were associated with limbal granulomas but the peripheral corneal ulcerations were not as se-

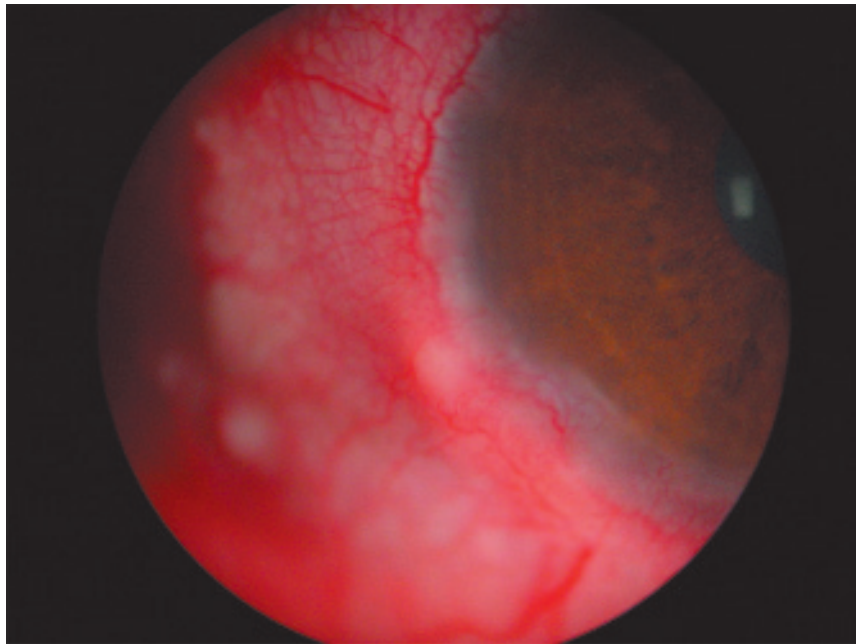


Fig 2. Limbal granuloma.

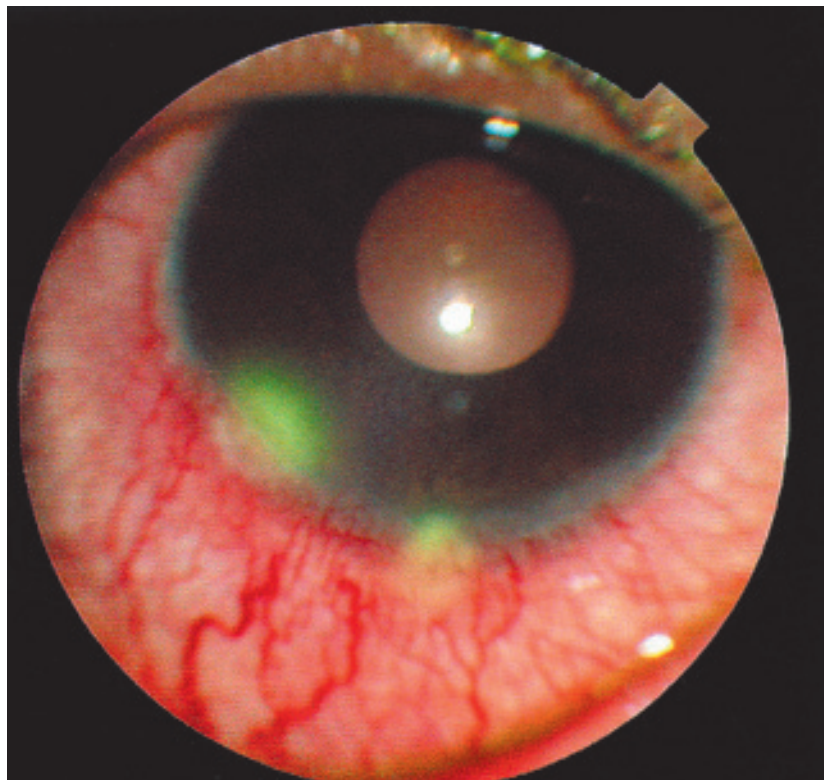


Fig 3. Peripheral ulcerative keratitis.

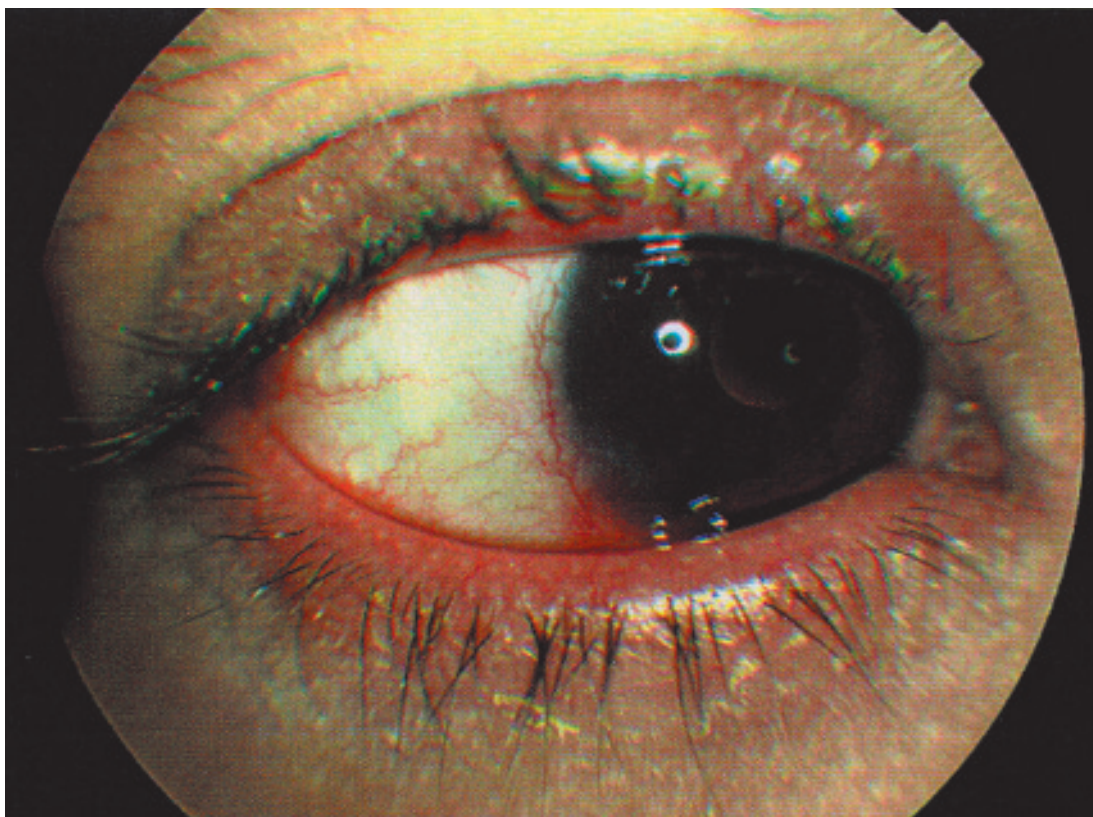


Fig 4. Staphylococcal blepharitis.

vere as the initial presentation. However it was striking that the corneal lesions occurred at the same time as the limbal granulomas and were situated in the adjacent cornea. The recurrences responded promptly to topical treatment as described above. Once epithelialization had occurred, treatment was changed to maintenance with fluorometholone 0,1% oid continuously. Discontinuation rapidly led to recurrence of redness and soreness in the eyes, so she preferred to take fluorometholone on an infrequent but regular basis, increasing frequency if the eye signs or symptoms recurred.

In addition to these dramatic flare ups of external disease, she also developed episodic symptoms from severe mixed staphylococcal blepharitis and meibomian gland dysfunction. These episodes were not associated with marginal keratitis and responded to treatment with lid hygiene and occasional courses of fucithalmic gel 1% applied topically to the lids following bathing with warm water.

On her last review, four years after presentation, slitlamp examination revealed chronic blepharitis and meibomian gland disease, with some conjunctival reaction (Figure 4-5). The peripheral cornea shows inactive vascularisation at the site of previous ulcerations, and there is no fluorescein staining. She is maintained on oral doxycycline 50mg bid and fluorometholone drops oid to both eyes. On this regime she had no recurrence of keratitis for over one year. For the cutaneous disease she is currently using oral ciprofloxacin 500mg bd, itraconazole 100 mg oid and co-trimoxazole 960 mg oid and applies an antiseptic soap substitute to the skin. The skin and lids have greatly improved on this treatment. Subjectively, the patient thinks that her condition is under control and looks the best it has done for years. She is not keen to decrease the combination of antibiotics as she fears that her skin or eyes will flare.

Interferon-gamma has been proposed as an adjuvant treatment to stimulate the immune sys-

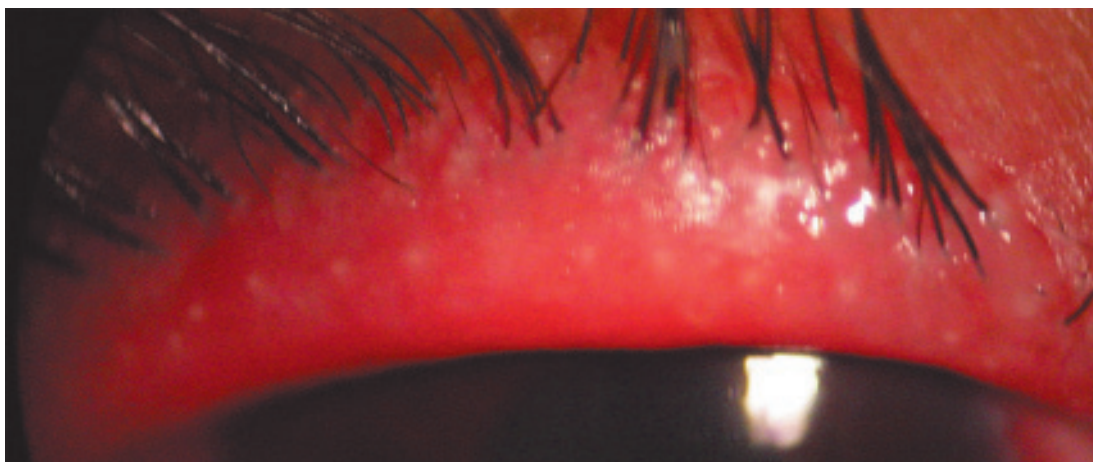


Fig 5. Meibomian gland disease.

tem in this condition. Though this immunosuppressive treatment has proven to be successful, our patient is not keen on pursuing this therapeutic option, as she is pleased with the response that has been achieved with antimicrobial therapy and because of the possible side-effects of interferon-gamma (2,12,18,20).

DISCUSSION

CGD is a rare (1 in 200,000 live births) congenital immunological disorder, caused by impaired phagocyte killing due to dysfunction of any of the components of the reduced NADPH oxidase (5,9,21). Four major subtypes have been identified, all with deficient NADPH oxidase function (Table 1). A fifth genetic disorder, deficiency of glucose-6-phosphate dehydrogenase, an X-linked enzyme that regulates the hexose monophosphate shunt, can very rarely result in CGD. A sixth genetic protein defect, Rac2 mutation, has also been described as a cause of variant CGD, though its clinical presentation appears closer to that of leucocyte adhesion defect or neutrophil actin dysfunction (9,16). Our patient has the less severe Variant CGD subtype which is due to p67^{phox} deficiency and is inherited as an autosomal recessive trait. The X-linked recessive subtype is more severe with earlier age of diagnosis and death compared with autosomal recessive disease. Patients may present with recurrent infections caused by a specific subset of catalase producing bacteria or fungi, including *Staphylococ-*

cus Aureus, *Serratia Marcescens*, *Burkholderia Cepacia*, and *Nocardia* and *Aspergillus* species (9). Recurrent infections in patients with CGD are most often due to new infection, rather than relapse of pre-existing infection (7). Published evidence exists of granulomatous inflammation of the choroid, retina and sclera in patients with CGD (10,17,19). A vascular orbital lesion was described in CGD (1). Keratitis caused by *Candida glabrata* has been reported (4). Immunodeficient patients are known to have a higher incidence of lid and conjunctiva infection, though the microbial flora of the lids and conjunctiva does not seem to differ from age-matched controls (6). In patients with neutrophil dysfunction, a higher incidence of blepharokeratoconjunctivitis has been reported. Abnormal neutrophil function probably interferes with the control of normal eyelid and predisposes the eye to the development of staphylococcal blepharitis and subsequently marginal keratitis due to staphylococcal hypersensitivity (13). To the best of our knowledge, this is the first reported case of limbal granuloma associated with CGD. This clinical finding has not yet been confirmed by a biopsy, because of the rapid response to treatment.

Table 1: Major subtypes of CGD.

	NADPH oxidase components			
	Gp91 ^{phox}	P22 ^{phox}	P47 ^{phox}	P67 ^{phox}
Frequency	70%	5%	20%	5%
Inheritance	X-linked	AR	AR	AR
Gene Location	Xp21.1	16q24	7q11.23	1q25

In our patient the keratitis was severe and associated with deep ulceration (peripheral ulcerative keratitis), an appearance distinct from the marginal infiltrates seen as a hypersensitivity to staphylococci in blepharitis patients (15). The association of this patients peripheral ulcerative keratitis in time and place with elevated limbal granulomas suggests a local causation, perhaps mediated by inflammatory products and collagenases derived from cells within the granulomas. Thus the corneal lesions in this patient would appear to have a similar etiology to the peripheral ulcerative keratitis caused by Mooren's ulcer (3,14). Since she responded to treatment, biopsy of the granulomas was not considered to be in her interest.

Nevertheless, the fact that this patient also has significant staphylococcal blepharitis means that it is possible that indirect hypersensitivity could also play a role in generating the peripheral keratitis. However marginal keratitis associated with blepharitis is characterised by marked infiltration and rarely by ulceration, certainly not by severe deep peripheral ulcerative keratitis (15).

CONCLUSION

CGD can be associated with limbal granulomas and adjacent keratitis. Such lesions can be successfully treated with intensive topical antibiotic and steroid treatment and a multidisciplinary approach is important for long term management of remission.

REFERENCES

- (1) ANDERSEN S.R. – Vascular lesion (arteriovenous aneurysm or haemangioma) of the orbit in a case of chronic granulomatous disease. *Ophthalmologica* 1976; 173:145-51.
- (2) BEMILLER L.S., ROBERTS D.H., STARKO K.M., CURNUTTE J.T. – Safety and effectiveness of long-term interferon gamma therapy in patients with chronic granulomatous disease. *Blood Cells Mol Dis*. 1995; 21:239-47.
- (3) BROWN S. – Mooren's ulcer. Histopathology and proteolytic enzymes of adjacent conjunctiva. *Br J Ophthalmol* 1975; 59:670-674.
- (4) DJALILIAN A.R., SMITH J.A., WALSH T.J., MALECH H.L., ROBINSON M.R. – Keratitis caused by *Candida glabrata* in a patient with chronic granulomatous disease. *Am J Ophthalmol* 2001; 132:782-3.
- (5) DOHIL M., PRENDIVILLE J.S., CRAWFORD R.I., SPEERT D.P. – Cutaneous manifestations of chronic granulomatous disease. Report of 4 cases and review of the literature. *J Am Acad Dermatol* 1997; 36:899-907.
- (6) FRIEDLAENDER M.H., MASI R.J., OSUMOTO M., SMOLIN G., AMMANN A.J. – Ocular microbial flora in immunodeficient patients. *Arch Ophthalmol*. 1980; 98:1211-3.
- (7) GUIDE S.V., STOCK F., GILL V.J., ANDERSON V.L., MALECH H.L., GALLIN J.I., HOLLAND S.M. – Reinfection, rather than persistent infection, in patients with chronic granulomatous disease. *J Infect Dis* 2003; 187:845-853.
- (8) HUMBERT J.R., FISHMAN C.B., WESTON W.L., DEARMEY P.A., THOREN C.H. – Frequency of the carrier state for X-linked chronic granulomatous disease among females with lupus erythematosus. *Clin Genet*. 1976; 10:16-20.
- (9) JOHNSTON R.B.Jr. – Clinical aspects of chronic granulomatous disease. *Curr Opin Hematol* 2001; 8:17-22.
- (10) LISCHNER H.W., MARTYN L.J. – Chorioretinal lesions, sea-blue histiocytes and other manifestations in familial chronic granulomatous disease. *Birth Defects Orig Artic Ser*. 1975; 11:73-6.
- (11) LOVAS J.G., ISSEKUTZ A., WALSH N., MILLER R.A. – Lupus erythematosus-like oral mucosal and skin lesions in a carrier of chronic granulomatous disease. Chronic granulomatous disease carrier genodermatosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995; 80:78-82.
- (12) MALMVALL B.E., FOLLIN P. – Successful interferon-gamma therapy in a chronic granulomatous disease patient suffering from *Staphylococcus aureus* hepatic abscess and invasive *Candida albicans* infection. *Scand J Infect Dis* 1993; 25:61-6.
- (13) PALESTINE A.G., MEYERS S.M., FAUCI A.S., GALLIN J.I. – Ocular findings in patients with neutrophil dysfunction. *Am J Ophthalmol*. 1983; 95:598-604.
- (14) REZA M.M., SHERIDAN L. – The ocular immune response. *Diseases of the cornea*. Missouri, St Louis, USA: CV Mosby Company, 1979; 6:114.
- (15) REZA M.M., SHERIDAN L. – Phlyctenular Keratoconjunctivitis and Marginal Staphylococcal Keratitis. *Diseases of the cornea*. Missouri, St Louis, USA: CV Mosby company 1979; 109:1392-1394.

- (16) SEGAL B.H., LETO T.L., GALLIN J.I., MALECH H.L., HOLLAND S.M. – Genetic, biochemical, and clinical features of chronic granulomatous disease. *Medicine* 2000; 79:170-200.
- (17) SEONG-JOON K., JOONG GON K., YOUNG SUK YU – Chorioretinal lesions in patients with chronic granulomatous disease. *Retina* 2003; 23:360-365.
- (18) TODD P.A., GOA K.L. – Interferon gamma-1b. A review of its pharmacology and therapeutic potential in chronic granulomatous disease. *Drugs* 1992; 43:111-22.
- (19) VALLURI S., CHU F.C., SMITH M.E. – Ocular pathologic findings of chronic granulomatous disease in childhood. *Am J Ophthalmol* 1995; 120:120-3.
- (20) WEENING R.S., LEITZ G.J., SEGER R.A. – Recombinant human interferon-gamma in patients with chronic granulomatous disease. European follow-up study. *Eur J Pediatr.* 1995; 154:295-8.
- (21) WINKELSTEIN J.A., MARINO M.C., JOHNSTON R.B. Jr., BOYLE J., CURNUTTE J., GALLIN J.I., MALECH H.L., HOLLAND S.M., OCHS H., QUIE P., BUCKLEY R.H., FO C.B., CHANOCK S.J., DICKLER H. – Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine* 2000; 79:155-69.
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