

## ERYTHEMA NODOSUM: PROSPECTIVE STUDY OF 32 CASES

Nurimar C. FERNANDES (1), Juan MACEIRA (2) & Mauro de Medeiros MUNIZ (3)

---

### SUMMARY

The results of 32 cases studied lead us to the conclusion that erythema nodosum's investigation routine is very important, once in our retrospective study, the percentage of cases of unknown etiology was 69.4%, and in this prospective study it is 21.8%. In 10 cases (31.2%), more than one causing agent was suspected. Infections (bacterial, helminthic, fungal, by protozoa) were diagnosed in 26 cases, streptococcal infection having predominated (12 cases). Drugs-dipirone, aspirin, anovulatory - were suspected as causing agents in 13 cases. The association of erythema nodosum and histoplasmosis capsulata is described for the first time in Brazil. We consider erythema nodosum to be a complex syndrome which should be regarded as a manifestation of underlying diseases. The fact that all 32 subjects were women, 26 of them during menacme, suggests that particular hormonal media may favor the action of various processes (infections and drugs), precipitating erythema nodosum's clinical picture.

**KEYWORDS:** Erythema nodosum; Histoplasmosis capsulata.

---

### INTRODUCTION

Erythema nodosum is a nodular painful syndrome which results from a hypersensitivity reaction to various possible antigenic stimulus, and forms immune complexes that deposit in dermi's venules. It appears in the course of various diseases as well as during therapeutics<sup>4,32</sup>. The clinical picture is always that of a non-specific systemic disease with malaise (67%), arthralgias (64%), low fever (60%), and arthritis (31%). However, it may be overcome by the presentation of an associated disease. The laboratorial tests show no abnormalities except for those related to an underlying disease. Treatment of the idiopathic form includes non-steroidal anti-inflammatory drugs which relieve discomfort (Fig. 1).

Steroids are not recommended due to erythema nodosum's benign nature and to the risk of dissemination of an accompanying illness.

In typical cases, the affection is well defined, develops in the course of one month, and then disappears. During this period, it may present recurrence with the appearance of new lesions. The painful nodules vary in number (from 3 to 40) and may come together into plaques; they are red violet color, brilliant, and are located on the tibial crest, feet, knees, internal surface of the thighs, buttocks and sometimes forearms. In the regressive stage they resemble contusions and heal without scarring.

---

(1) Adjunt Professor of Dermatology, Faculdade de Medicina da Universidade Federal do Rio de Janeiro, Hospital Universitário Clementino Fraga Filho.

(2) Adjunt Professor of Pathology, Faculdade de Medicina da Universidade Federal do Rio de Janeiro, Hospital Universitário Clementino Fraga Filho.

(3) Mycology Laboratory, Hospital Evandro Chagas - FIOCRUZ.

**Correspondence to:** Nurimar C. Fernandes, Rua Alexandre de Gusmão, 28 apto. 201, 20520-120 Tijuca - Rio de Janeiro, RJ, BRASIL.



Fig. 1 - Tender, nodular lesions located over the extensor surfaces of the legs.

Some published series show that percentages of erythema nodosum with unknown etiology vary (Table 1).

Sarcoidosis appears with greater frequency in James' (74%) and Hannuksela's (47%) publications. Tuberculosis is found in variable proportions in the referred reports (Table 1). Its greatest incidence is in Gordon's group (20%), probably because it includes children.

**TABLE 1**  
Erythema nodosum: comparison between reported series.

Author/Year	Year	N. of cases	Etiology	
			Known	Unknown
Vesey $\alpha$				
Wilkinson	(1959)	70	67 (96%)	3 (4%)
Gordon	(1961)	115	61 (53%)	54 (47%)
James	(1961)	170	147 (86%)	23 (14%)
Hannuksela	(1971)	343	268 (78%)	75 (21%)
Folch	(1978)	50	38 (76%)	12 (24%)
Monreal	(1983)	68	37 (54%)	31 (45%)
Lario	(1987)	103	54 (52.4%)	49 (47.5%)
Wanke	(1989)	72	22 (30.5%)	50 (69.4%)

Streptococcal infection was the most frequent cause in the series of MONREAL et al. (23.2%), LARIO et al. (22.3%) and FOLCH et al. (30%). In VESEY and WILKINSON'S report, sarcoidosis and streptococcal infection appear in equal proportions (45.6%).

According to LARIO et al., in up to 20% of patients with streptococcal pharyngitis, elevation of titers of antistreptolysin 0 is not observed, and therefore some cases catalogued as of unknown etiology would in reality be post-streptococcal. He observed that in almost one third of these patients, pharyngitis and tonsillitis is immediately preceded the case.

Various publications turn evident the wide possibilities of different affections, as well as vaccines, to cause erythema nodosum<sup>1, 2, 3, 5, 6, 9, 10, 11, 12, 13, 14, 15, 21, 22, 25, 26, 31, 36, 39, 40, 41, 46</sup>. It seems clear that erythema nodosum is far from having detected all of its underlying diseases. In North America, the association between *Histoplasma capsulatum* and erythema nodosum is well known. The diagnosis of 43 cases of histoplasmosis in the short time interval of 2 years (1981-1982) in Rio de Janeiro State, taking into account that to this date 111 cases were registered in Brazilian medical literature, shows the importance of this disease in our country and that most certainly many cases are not diagnosed<sup>44</sup>. We carried out a systematical prospective study of erythema nodosum's etiologic agents, considering the lack of ample studies in Brazilian medical literature.

## PATIENTS AND METHODS

Thirty-two patients with erythema nodosum were studied in Clementino Fraga Filhos's University Hospital, Federal University of Rio de Janeiro, in the period of January 1990 to January 1993. All patients were submitted to the following routine:

1. detailed anamnesis and physical examination
2. red and white blood cell counts and erythrocyte sedimentation rate
3. urinalysis
4. routine stool examination (3 samples)
5. evaluation of antistreptolysin 0
6. bacteriological examination of swab of the oropharynx
7. tuberculin skin test<sup>8</sup>: The tuberculin employed (PPD-RT 23) was applied according to technique recommended by WHO, by intradermic via, on the anterior part of the left forearm, in a 0.1 ml dose

equivalent to 2 TU (tuberculin units). Seventy-two hours after application, induration on the application point was searched for by palpation. Transverse diameter of induration area was measured with a millimeter-scaled ruler.

INDURATION DIAMETER	CLASSIFICATION	INTERPRETATION
5mm	non reactor	not infected, anergic
5 to 9 mm	weak reactor	infected by BK, atypical mycobacteria or vaccinated with BCG
10 mm	strong reactor	infected, with or without the disease, vaccinated with BCG

8. Mitsuda's Test <sup>7</sup>

The antigen was prepared by grinding of lepromas from virchowian patients-Human Mitsudina-FioCruz.

**Application Technique.**

0.1 ml of the antigen were injected by intradermic via on the anterior surface of the right forearm, 2 to 3 cm below the antecubital fold. A papule of approximately 1 cm was formed in the inoculation point. Interpretation of results for Mitsuda's delayed reaction after 21 days followed WHO criteria (1970).

**Negative:** absence of tubercle

**Positive:** tubercle with the size of 5 mm or more, ulceration.

9. chest X-Ray

10. quantitative VDRL Test

11. biopsy of nodule: the histopathological pattern considered was that of septal panniculitis.

12. serologic test for *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*' soluble antigens by double immunodiffusion in agar, performed in Mycology Laboratory of Evandro Chagas' Hospital - FioCruz.

As a serologic technique, double immunodiffusion in agar has shown great sensibility and total specificity, besides performance simplicity: in this test, two precipitation bands, designated M and H bands, are valuable for histoplasmosis diagnosis. Band M indicates recent infection and appears in approximately 50% of the cases. Band H is less sensible and indicates infection activity with certainty. The appearance of M band in paired sera of convalescent patients is diagnostic of acute disease (Fig. 2).

Various dilutions of standard antigen (1:2, 1:4, 1:8, etc...) diffuse in gel (24-48 hours) against specific antiserum. Patient's serum also diffuses in Ouchterlony's plate. Serum's titer is obtained by comparison with migration of standard antigen; it corresponds to the greatest antigen dilution which present a well defined positive band analogous to that of serum and the same number of precipitation lines <sup>44</sup>.

13. Patients were followed in an outpatients' basis for six months to 1 year for evaluation of therapy results of the basic clinical pictures and/or recidivation. The appropriate laboratory tests were repeated in this period till negatvation or normalization.

**ETHICAL ASPECTS**

Procedures <sup>2, 3, 4, 5, 6, 7, 8, 9, 10, 11</sup> constitute etiology investigation routine and are therefore diagnostic tests. Histoplasmosis' specific serology implied in collection of a 10 ml blood sample, which was repeated in a 6-month time interval in case the first had been reactive. Once this is considered minimum risk research (National Health Council, Resolution n.1, 13<sup>th</sup> June 1988, Chapter 1, article 7, item 2) Ethics' Committee permitted the acquirement of post-information authorization without written formulation. (National Health Council, Resolution n.1, 13<sup>th</sup> June 1988, Chapter I, Article 13).

**RESULTS**

All cases studied were in women and distributed

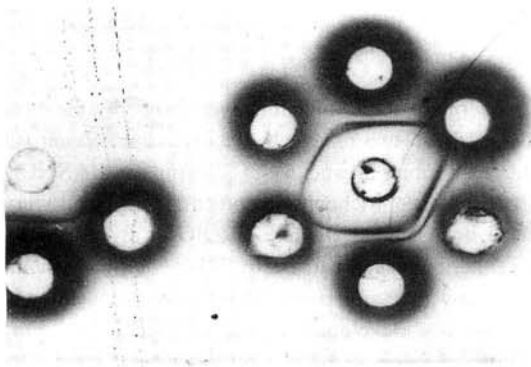


Fig. 2 - Serologic diagnosis of histoplasmosis: double immunodiffusion in agar (M and H bands).

mainly in the age range of 20-29 years (8 cases) and 40 - 49 years (9 cases) (Table 2).

**TABLE 2**  
Distribution of cases according to age range.

Age range	Number of cases
10 - 19	3
20 - 29	8
30 - 39	5
40 - 49	9
50 - 59	3
60 - 69	4
Total	32

As to etiology, causing factors were detected in 15 cases and in 10 cases, more than one factor was suspected; in 7 cases, etiology remained unknown (Table 3). Cases were grouped according to causing agents (Table 4 and 5).

### DISCUSSION

In 7 cases ( 21.8%) no conclusion was drawn out from the proposed investigation routine. Of these cases, only 3 presented recurrence in the observed period (Table 3).

**TABLE 3**  
Distribution of cases according to the number of probable etiologic factors.

Number of etiologic factors	Number of cases
one	15 (46.8%)
more than one	10 (31.2%)
none	7 (21.8%)
Total	32 (99.8%)

Drugs suspected as causing factors were dipirone (8 cases), aspirin (2 cases) and anovulatorys (3 cases) (Table 4 and 5). Some decades ago antipyretics were considered potential causers of erythema nodosum <sup>23</sup>. Since dipirone possesses a similar radical (phenazone) as antipyrine, a pyrazolonic product listed as causing agent, we considered appropriate to include it among the causes of the disease.

Several authors acknowledged a hormonal factor in erythema nodosum's pathogenesis <sup>20, 28, 33</sup>. It is yet

debated whether hormones, especially estrogens, increase individual susceptibility to another factor or causing agent the percentage of women included in erythema nodosum's series varies between 75 to 90%, the majority in menacme; for some authors, these are indications that there is a relationship between the appearance of the clinical picture, anovulatory ingestion and pregnancy <sup>6, 20, 28, 33</sup> (Table 5).

In 12 cases high levels of antistreptolysin 0 point to streptococcal infection and in 1 case, isolation of *Escherichia coli* points to urinary infection (Table 4 and 5). *MONREAL* et al. <sup>28</sup> consider erythema nodosum's causing factor to be a streptococcal infection, under, the following circumstances: pharyngitis and tonsillitis, or streptococcal infection in another location in the body, three weeks before the appearance of erythema nodosum; antistreptolysin 0 titers above 250 U and/or positive culture for group A hemolytic streptococcus; antistreptolysin 0 titers above 500 U independent of the presence of a streptococcal clinical picture.

**TABLE 4**  
Distribution of cases according to one probable etiologic factor.

Etiologic factor	Number of cases
Dipirone	5
Streptococcus	3
Anovulatory	2
Aspirin	1
<i>Trichophyton rubrum</i>	1
<i>Escherichia coli</i>	1
<i>Trichomonas vaginalis</i>	1
Crohn's disease	1
Total	15

Gram negative <sup>10, 19, 22, 29, 31, 38, 39, 42</sup>, spiral <sup>1, 11, 12</sup> and strictly intracellular <sup>13, 14</sup> bacteria have been appointed as erythema nodosum's causing agents.

Dermatophytic infections were probably the cause of 3 cases, in two of which *Trichophyton rubrum* was isolated (Tables 4 and 5). According to HANNUKSELA <sup>20</sup>, deep trichophytic infection may cause erythema nodosum. MARTINEZ ROIG et al <sup>26</sup> described three kerion cases caused by *Trychophyton mentagrophytes*, that after 9 weeks of oral treatment with griseofulvin, developed typical erythema nodosum's nodules in lower limbs that resolved in 12 days.

Protozoans such as *Entamoeba histolytica* and

*Giardia lamblia* have been appointed as causing agents of erythema nodosum <sup>21</sup> these authors describe a case of association of invasive amebiasis giardiasis and speculate on which one of the two would have caused erythema nodosum. We believe that in 3 cases *Trichomonas vaginalis* could be the causing agent and *Giardia lamblia* in one case (Table 4 and 5).

The association of erythema nodosum and Crohn's disease diagnosed in one case (Table 4), has been referred to by several authors <sup>2, 25</sup>.

Erythema nodosum has been described in histoplasmosis. The majority of cases occur in Canada, Yowa and South Carolina, areas of low endemicity. It is estimated that one in two-hundred infections will be associated to erythema nodosum or erythema polymorphus <sup>16, 30</sup>. These are the most common cutaneous manifestations of histoplasmosis and are usually associated to acute histoplasmosis <sup>27, 37, 47</sup>, which is the most frequently diagnosed form of the infection. The majority of cases occur in individuals exposed to soil dust rich in birds' or bats' feces, who are contaminated with the fungus by inhalation of a great number of infecting particles. On the contrary to what occurs in the epidemic outbreaks, infection sources of isolated cases of acute histoplasmosis are frequently not identified and are rarely well characterized with isolation of the fungus. Even without the revolving of contaminated soil, fungus is capable of reaching and infecting a significantly great number of persons, in a 32 km radius around an infecting source under trees. It is therefore not surprising that our two positive serology cases did not relate to any suggestive epidemiological data (Fig. 2). Acute histoplasmosis presents symptoms and signs of an acute respiratory disease and the thoracic X-rays show pneumonic nodular infiltrating images, frequently accompanied with hilar thickening. The disease regresses spontaneously almost always. These two patients were asymptomatic.

Panniculitis associated to histoplasmosis was described by two authors: PARK <sup>34</sup> reported a renal transplantation with disseminated form that presented an erysipela-like clinical picture, whose histopathologic findings were of a panniculitis with absence of bacteria or fungus. An autopsy growth of *Histoplasma capsulatum* was seen in skin, bone, lungs, liver and pericardium. POTTAGE <sup>35</sup> described a case of mediastinal histoplasmosis, deficiency of alfa-1-antitrypsin and painful erythematous nodules of lower and upper limbs

and abdomen, which formed a fistula that drained a chestnut-brownish fluid, without odor. Histopathology showed lobular panniculitis. The patient presented an excellent response to ketoconazol.

Ascariasis was the probable causing factor in three cases, strongyloidiasis in one case and trichuriasis in another (Table 5). Erythema nodosum was reported in patients with helminthic infestations such as ascariasis and teniasis <sup>39</sup>. Syphilis is possibly related to erythema nodosum in 1 case (Table 5). The occurrence of erythema nodosum in syphilis has been recently reported in literature <sup>1</sup>.

**TABLE 5**  
Distribution of cases according to more than one probable etiologic factor.

More than one etiologic factor	Number of cases
Streptococcus - Dipirone	2
Streptococcus - Histoplasma capsulatum	1
Streptococcus - Ascaris lumbricoides	1
Streptococcus - Dermatophyte	1
Streptococcus - Treponema pallidum	1
Ascaris lumbricoides	
Streptococcus - Giardia lamblia - pregnancy	1
Trichophyton rubrum - aspirin - dipirone	1
Streptococcus - Trichomonas vaginalis	1
Strongyloides stercoralis - Histoplasma capsulatum	
Streptococcus - Trichomonas vaginalis	1
Ascaris lumbricoides - Trichuris trichiura	
Anovulatory	
Total	10

In the described cases, the infections and infestations were treated and in the 6 to 12 months follow-up, no recidivation of erythema nodosum was observed. In cases of histoplasmosis - *Histoplasma capsulatum* - serology was repeated every 3 months until it became non-reacting.

The suspected drugs were withdrawn and patients oriented to make use of acetaminophen.

In recent reviews, 2 or more causes for erythema nodosum were found in 19% <sup>20</sup> and 30% <sup>39</sup> of cases.

## CONCLUSIONS

The cases studied permit the following conclusions:

1. the investigation routine is extremely important

once in our retrospective study, the percentage of unknown etiology was 69.4% and in the present prospective study it is 21.8%.

2. 15 cases (46.8%) had a probable causing factor.
3. in 10 cases (31.2%) more than 1 etiologic agent was suspected.
4. the following infections and helminthic infestations were diagnosed in the Laboratory routine: streptococcal infection (12 cases), trichomoniasis (3 cases), dermatophytosis (3 cases), ascariasis (3 cases), urinary infection (1 case), syphilis (1 case), strongyloidiasis (1 case), giardiasis (1 case), trichuriasis (1 case).
5. the drugs suspected as causing agents were dipirone (8 cases), anovulatorys (3 cases) and aspirin (2 cases).
6. the association of erythema nodosum and histoplasmosis capsulata (2 cases) is described for the first time in Brazil.
7. erythema nodosum is a complex syndrome and should always be considered as a manifestation of underlying diseases, isolated or concurrent.
8. the fact that all subjects - 32 patients - were women, 26 of them during menacme, suggests that various processes (infections or drugs) may act in a particular and favorable hormonal media, precipitating erythema nodosum's clinical picture.

## RESUMO

### Eritema nodoso: estudo prospectivo de 32 casos

O estudo de 32 casos de eritema nodoso permite concluir que a rotina de investigação é extremamente importante já que em nosso estudo retrospectivo, o percentual de etiologia indeterminada foi de 69,4% e neste estudo prospectivo é de 21,8%. Em 10 casos (31,2%) mais de um agente causal foi suspeitado. Infecções (bacteriana, helmíntica, fúngica e por protozoário) foram diagnosticadas em 26 casos, tendo predominado a infecção estreptocócica com 12 casos. As drogas de suspeição foram dipirona, aspirina e anovulatório em 12 casos. A associação de eritema nodoso e histoplasmoze capsulata é descrita pela primeira vez no Brasil. O eritema nodoso é síndrome complexa e deveria ser considerado sempre como manifestação de doença subjacente. A amostra de 32 pacientes exclusivamente do sexo feminino sendo que 26 em idade fértil sugere que vários processos (infecções e drogas) podem atuar em meio hormonal, particular e favorecedor, precipitando o quadro de eritema nodoso.

## REFERENCES

1. ALINOV, A.; LUI, P. & BENOLD, D. - Syphilis-still a cause of erythema nodosum. *Int. J. Derm.*, 22: 310-311, 1983.
2. AREIAS, E. & GARCIA E SILVA, L. - Erythema nodosum and Crohn's disease. *Med. cut. ibero. lat. amer.*, 12: 489-495, 1984.
3. AREIAS, E. & GARCIA E SILVA, L. - Erythema nodosum and ulcerative colitis. *Acta med. port.*, 6: 143-147, 1985.
4. BONDI, E. E. & LAZARUS, G. S. - Panniculitis. In: FITZPATRICK, T. B.; EISEN, A. Z.; WOLFF, K.; FREEDBERG, J. W. & AUSTEN, K. F. - *Dermatology in general medicine*. 3. ed., New York, McGraw Hill, 1987. p. 1131-1148.
5. CASTILLA CORTAZAR, A.; PASTOR RODRIGUES, A. & AGUIRRE ERRASTI, C. - Erythema nodosum and Hodgkin's disease. *Med. clín. (Barcelona)*, 85: 431-1985.
6. CERVIA, M.; PARODI, A. & REBORA, A. - Chronic active hepatitis and erythema nodosum. *Arch. Derm.*, 118: 878, 1982.
7. CONTROLE DE HANSENÍASE - *Uma proposta de integração de ensino: serviço*. Rio de Janeiro, DNDS/NUTES, 1989.
8. CONTROLE DA TUBERCULOSE - *Uma proposta de integração ensino: serviço*. 2. ed. Rio de Janeiro, CNCT/NUTES, 1989.
9. DI GIUSTO, C. A. & BERNHARD, J. D. - Erythema nodosum provoked by hepatitis B vaccine. *Lancet*, 2: 1042, 1986.
10. DOBSON, H. M. & HUME, R. - Salmonella gastroenteritis associated with erythema nodosum. *Brit. med. J.*, 286: 1146, 1983.
11. EASTMOND, C. J. & REID, T. M. - *Campylobacter enteritis* and erythema nodosum. *Brit. med. J.*, 285: 1421-1422, 1982.
12. ELLIS, M. E.; POPE, J.; MOKASHI, A. & DUMBAR, E. - *Campylobacter colitis* associated with erythema nodosum. *Brit. med. J.*, 285: 937, 1982.
13. ERNTELL, M.; LJUNGGREN, K.; GADD, T. & PERSSON, K. - Erythema nodosum - a manifestation of *Chlamydia pneumoniae* (strain Twar) infection. *Scand. J. infect. Dis.*, 21: 693-696, 1989.
14. FOLCH, M. G.; BELESTEROS, F. & SAFFIE, P. - Eritema nodoso: experiência com 50 casos. *Rev. méd. Chile*, 106: 854-860, 1978.
15. GELLERT, A.; GREEN, E. S.; BECK, E. R. & RIDLEY, C. M. - Erythema nodosum progressing to pyoderma gangrenosum as a complication of Crohn's disease. *Postgrad. med. J.*, 59: 791-793, 1983.
16. GOODWIN, R. A.; LOYD, J. E. & DES PREZ, R. M. - Histoplasmosis in normal hosts. *Medicine*, 60: 231-266, 1981.
17. GOOLSBY, P. L. - Erythema nodosum after Recombivax HB hepatitis vaccine. *New Engl. J. Med.*, 321: 1198-1199, 1989.
18. GORDON, H. - Erythema nodosum. A review of one hundred and fifteen cases. *Brit. J. Derm.*, 73: 393-409, 1961.
19. GROSSMAN, M. E. & KATZ, B. - *Salmonella enteritidis* enterocolitis: another cause of diarrhea and erythema nodosum. *Cutis*, 34: 402-403, 1984.

20. HANNUKSELA, M. - Erythema nodosum with special reference to sarcoidosis. A clinical study of 343 Finnish adult patients. *Ann. clin. Res.*, 3 (supl. 7): 5-64, 1971.
21. HARRIES, A. D. & TAYLOR, J. - Erythema nodosum associated with invasive amoebiasis and giardiasis. *Brit. J. Derm.*, 114: 394, 1986.
22. IKEIA, T.; MIZUNO, E. & TAKAMA, H. - Three cases of erythema nodosum associated with *Yersinia enterocolitica* infection. *J. Derm.*, 13: 147-150, 1986.
23. JAMES, D. G. - Erythema nodosum. *Brit. med. J.*, 1: 853-857, 1961.
24. LARIO, B. A.; PINEY, E.; VALVERDE, V. R. & SAGREDO, J. L. P. - Eritema nodoso: estudo de 103 casos. *Med. clin. (Barcelona)*, 88: 5-8, 1987.
25. LLORENS-TEROL, J. & MARTINEZ-ROIG, A. - Erythema nodosum associated with infectious mononucleosis. *Helv. paediat. Acta*, 38: 91-94, 1983.
26. MARTINEZ-ROIG, A.; LLORENS-TEROL, J. & TORRES, J. M. - Erythema nodosum and kerion of the scalp. *Amer. J. Dis. Child.*, 136: 440-442, 1982.
27. MEDEIROS, A. A.; MARTY, S. D.; TOSH, F. E. & CHIN, T. D. Y. - Erythema nodosum and erythema multiforme as clinical manifestations of histoplasmosis in a community outbreak. *New Engl. J. Med.*, 274: 415-420, 1966.
28. MONREAL, J. M. & DE LA SERNA, A. R. - Eritema nodoso. Revisión de 68 casos. *Rev. clín. esp.*, 6: 405-408, 1983.
29. MONTEJO BARANDA, M.; GONZALES DE ZARATE APINANIZ, P.; PASCUAL VELASCO, F. & AGUIRRE ERRASTI, C. - Erythema nodosum associated with gastroenteritis caused by *Salmonella enteritidis*: a new case. *Med. clin.*, (Barcelona), 81: 412-413, 1983.
30. MORENO, A. J.; WEISMAN, I.; KENNEY, R. L. & FORT, S. L. - Concurrence of erythema multiforme and erythema nodosum. *Cutis*, 31: 275-278, 1983.
31. MORRISON, W. M.; MATHESON, J. A.; HUTCHINSON, R. B. & MACK, R. H. - *Salmonella gastroenteritis* associated with erythema nodosum. *Brit. med. J.*, 286: 765, 1983.
32. MOSCHELLA, S. L. - Hypersensitivity and miscellaneous inflammatory disorders. In: MOSCHELLA, S. L.; PILLSBURY, D. M. & HURLEY, H. J. *Dermatology*. Philadelphia, W. B. Saunders, 1975. p. 385-408.
33. PARET MASANA, A.; SABRIA LEAL, M.; FERRANDO BARBERA, J. & REY-JOLY BARROSO, C. - Erythema nodosum and pregnancy. *Rev. clín. esp.*, 182: 236-237, 1988.
34. PARK, R. K.; GOLTZ, R. W. & CAREY, T. B. - Unusual cutaneous infections associated with immunosuppressive therapy. *Arch. Derm.*, 95: 345-350, 1967.
35. POTTAGE, J. C.; TRENHOLME, G. M.; ARONSON, I. K. & HARRIS, A. A. - Panniculitis associated with histoplasmosis and alpha 1 - antitrypsin deficiency. *Amer. J. Med.*, 75: 150-153, 1983.
36. SCHVED, J. F.; BENOIST D'AZU, G.; BRUNEL, M. & VALLAT, G. - Hairy cell leukemia associated with tuberculosis, disclosed by erythema nodosum. *Sem. Hôp. Paris*, 59: 2716-2717, 1983.
37. SELLERS Jr., T. F.; PRICE Jr., W. N. & NEWBERRY Jr., W. M. - An epidemic of erythema multiforme and erythema nodosum caused by histoplasmosis. *Ann. intern. Med.*, 62: 1244-1262, 1965.
38. STECKELBERG, J. M.; TERRELL, C. L. & EDSON, R. S. - Laboratory-acquired *Salmonella typhimurium enteritis*: association with erythema nodosum and reactive arthritis. *Amer. J. Med.*, 85: 705-707, 1988.
39. TAMI, L. F. - Erythema nodosum associated with *Shigella colitis*. *Arch. Derm.*, 121: 590, 1985.
40. TEYSSANDIER, R.; GUIDET, B.; PINTA, P. & OFFENSTADT, G. - *Mycoplasma pneumoniae pneumopathy* with severe anemia and erythema nodosum. *Presse méd.*, 14: 1613, 1985.
41. VARELA ALONSO, C.; SANTILLANA LOPEZ, I.; DE ANDRES DE COLSA, R.; RUIZ DE AGUIAR & GONZALEZ, A. - Erythema nodosum in brucellosis. *Med. clin.*, (Barcelona), 91: 437, 1988.
42. VERDEJO ORTES, J.; POLO RODRIGUEZ, R. M.; FENOY RODRIGUEZ, P. A. & GONZALEZ LAHOZ, J. M. - Erythema nodosum associated with *Salmonella enteritidis gastroenteritis*. *Rev. clín. esp.*, 178: 151, 1986.
43. VESSEY, C. M. R. & WILKINSON, D. S. - Erythema nodosum. A study of seventy cases. *Brit. J. Derm.*, 71: 139-155, 1959.
44. WANKE, B. - *Histoplasmose: estudo epidemiológico, clínico e experimental*. Rio de Janeiro, 1985. (Tese de doutoramento - Faculdade de Medicina da Universidade Federal do Rio de Janeiro).
45. WANKE, N. C. F.; FERNANDEZ, L. & BONAT, E. F. - Eritema nodoso: revisão de 72 casos. *An. bras. Derm.*, 64: 23-24, 1989.
46. WEINSTEIN, A.; BUJAK, D.; MITTELMAN, A. & DAVIDIAN, M. - Erythema nodosum in a patient with renal cell carcinoma treated with interleukin 2 and lymphokine activated killer cells. *J. Amer. med. Ass.*, 258: 3120-3121, 1987.
47. WHEAT, L. J.; SLAMA, T. G.; EITZEN, H. E. et al. - A large urban outbreak of histoplasmosis. Clinical features. *Ann. intern. Med.*, 94: 331-337, 1981.

Recebido para publicação em 16/03/1994  
Aceito para publicação em 13/07/1994