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Pyoderma gangrenosum of the "sinus mammarum" in ulcerative colitis

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SUMMARY: Pyoderma gangrenosum of the "sinus mammarum" in ulcerative colitis.

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The first part of this article deals with the report of a patient suffering from pyoderma gangrenosum of the "sinus mammarum" associated with asymptomatic ulcerative colitis. This is followed by a revision of the present epidemiological, etiological, pathogenetic and clinical knowledges about this systemic manifestation of chronic phlogosis of the colon.

The Authors have analysed the treatment for this condition and emphasized the resistance of the cutaneous ulcer encountered to conventional medical therapy of the underlying colonic disease which proved to be efficacious only on the latter; this led to integrate traditional treatment with the use of perilesional injections of small doses of calcic heparin as an alternative to immunosuppressive drugs or surgery. Topical antithrombotic treatment, which can be justified by the histological findings of phenomena of the vasculitis in the edge of pyoderma gangrenosum, demonstrated to be crucial and represents a peculiarity in the case here reported, which is unique in the literature as far as the Authors know, since it has not been experimented by anyone else.

RIASSUNTO: Pioderma gangrenoso del "sinus mammarum" in corso di colite ulcerosa.

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Gli Autori, prendendo spunto dall'osservazione di una paziente con pioderma gangrenoso del "sinus mammarum" in corso di colite ulcerosa asintomatica, fanno una revisione delle attuali conoscenze epidemiologiche, eziopatogenetiche e cliniche su questa manifestazione sistemica della flogosi cronica del colon.

Essi ne analizzano, inoltre, l'approccio terapeutico e sottolineano la refrattarietà dell'ulcera cutanea alla convenzionale terapia medica della malattia colica sottostante, efficace in effetti solo per questa, che li conduce, in alternativa a trattamenti immunosoppressivi o all'opzione chirurgica, ad associare l'impiego di iniezioni perilesionali di piccole dosi di eparina calcica. Il trattamento topico antitrombotico, che trova il suo razionale nel riscontro istologico di fenomeni vasculitici a carico dei margini del pioderma gangrenoso, si dimostra risolutivo e rappresenta una peculiarità del caso clinico illustrato, unico in letteratura a quanto è dato di sapere, non essendo stato da altri sperimentato.

KEY WORDS: Ulcerative colitis - Extraintestinal complications - Pyoderma gangrenosum.
Colite ulcerosa - Complicazioni extraintestinali - Pioderma gangrenoso.

Introduction

As far as the alimentary canal is concerned, ulcerative colitis (UC) is by definition an organ disease in the sense that it does not go beyond the limits of the colon-rectum area; all the same, in 14-36% of cases, during the course of the illness, extraintestinal complications can be observed in tissues and organs apart from the colon-rectum, which is without doubt an important prognosis factor because of its important contribution to the morbidity and mortality of the patients (12, 22, 56, 71).

The spectrum of extracolonic diseases that can be linked to UC include - in decreasing order of frequency: osteo-articular lesions (seronegative polyarthrititis, ankylosing spondylitis, sacroileitis), cutaneous (nodosum erythema, pyoderma gangrenosum, papulonecrotic lesions and vesiculopustular, polymorphic erythema, aphthous ulcerations), hepatobiliary (pericolangitis, hepatitis, cirrhosis, sclerosing cholangitis), ocular (uveitis, iritis, episcleritis) and a wide range of renal, vascular and haematological complications (1, 12, 22, 56).

The incidence of unhealthy skin disorders in patients with UC oscillates between 1.7% and 34% (3, 5, 20, 22, 26, 30, 59); the worst of these is pyoderma gangrenosum (PG), an inflammatory, necrotizing, ulcerative skin disease, first reported in 1929 by Bargen (2).

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Fig. 1- The ulcerative lesion - A. On the patient's arrival in the ward; B. On the sixth day of hospitalization; C. On the day after topical antithrombotic treatment. There are some small petechias in the sites of the perilesional injections of calcic heparin; D. On the 36th day from the beginning of topical antithrombotic treatment (the perilesional injections of calcic heparin were carried out on alternate days only during the first 24 days). Signs of positive change are evident: reduced dimensions and trophic edges; E. On the 48th day from the beginning of topical antithrombotic treatment (the perilesional injections of calcic heparin were carried out on/in alternate days only during the first 24 days). At the moment there is a serpiginous scar, with skin atrophy and dyschromia; there is still some very superficial area of cruentation.

We consider worthy of note the case of a patient with PG associated to UC; the UC condition was not obvious at the onset of the cutaneous lesion which was in fact the initial manifestation of it. This example enriches the case-record of extraintestinal complications of UC and it is also important because of the unusual place of the onset of PG - the "sinus mammarum". Other important aspects are the light-to-moderate seriousness and the limited extension of the underlying disease, the resistance of the PG to conventional medical treatment of UC, to which the UC responds, and the fact that we obtained results with the additional use of perilesional injections of small doses of calcic heparin instead of immunosuppressive drugs or surgery. The additional, topical antithrombotic treatment, based on the histological findings of phenomena of the vasculitis in the edge of the cutaneous ulcer, represents a peculiarity in our case, which is unique in the literature as far as we know, since it has not been experimented by anyone else.

Case report

B.E., a 36-year-old married housewife with children, was admitted to our ward with the diagnosis of "ulcerative lesion of the sternum area".

The family, physiological and distant pathological background did not show any important information nor did they show up pathologies worthy of note.

The patient dated the onset of the disease to about 15 days before, going into hospital when she noted the appearance between her breasts of a nodule the shape and size of a large grain of rice, covered with reddened edematous skin, which was hard and pain-

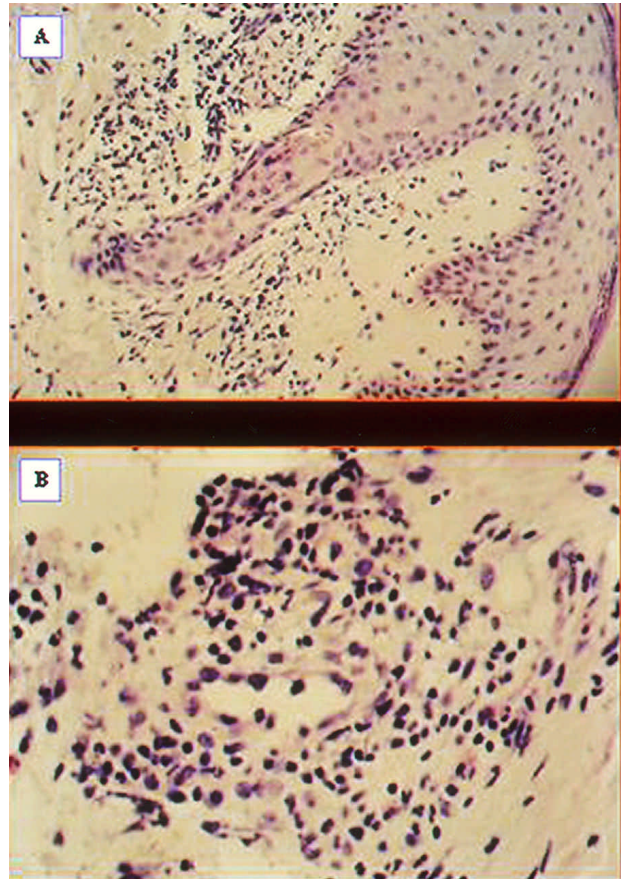


Fig. 2 - A and B - Biopsy specimen from the edge of ulcerative lesion demonstrates a substantial inflammatory infiltrate in the papillary dermis, mainly around the vessels; this is prevalently formed of lympho-histiocytic elements and acidophytes.

ful both spontaneously and to the touch. At first she thought it was the beginning of a boil and was further convinced of this idea when the initial lesion subsequently changed into a protruding pustule and the secondary spontaneous draining of this produced purulent material.

Over the next few days the patient noticed that a scab did not form, which is usually part of the healing process of a boil, but that there was the residue of an ulcer which was still particularly painful and which spread rapidly until it reached its present size, despite the unspecified topical treatment prescribed by the family doctor.

After an examination of the patient, who was generally in reasonable health, no pathological elements emerged which are worth mentioning, apart from a clear state of anxiety and depression, which a careful psychological examination of the patient revealed that this seems to have existed before the onset of the cutaneous lesion and to have been motivated by a degeneration of marital relations. We focussed our attention on the ulceration in the "sinus mammarum" which had extended asymmetrically towards the left breast. The oval-shaped lesion, with a larger transversal diameter measured about 6x5 cm; it had thin, frayed cribrate edges with openings from which creamy puruloid material oozed, sometimes coagulated and stuck to the bottom, not bleeding, soft and painful to the touch, undermining and formed of atrophic skin, prone to necrotic phenomena, cyanotic purple in colour, surrounded by haloes of erythematous skin; the base, formed by the sub-cutaneous, was red-orange coloured, mameelonated and moist because of sero-torbid secretions (Fig. 1A).

The routine laboratory investigations indicated hypochromic-hyposideremic anaemia (RBC 4.060.000/mm³; haemoglobin 10.5g%; hematocrit 26%; sideraemia 32 ng/dl) and leukocytosis with a movement towards the left of the formula (WBC 13.400/mm³; 82% of neutrophils); thrombocytosis was present (PLT 565.000/mm³). Serum protein electrophoresis showed a decrease of total proteins (4.9 g/dl) and albumin levels (42.8%) and an increase of alpha 1 - (8.7%) and alpha2-globulin (16.9%). Serum electrolytes levels and hepatic and renal functional activity were all within the normal range. Aspecific indices of phlogosis appeared to have increased (ESR 45 in the first hour; CRP 20.5 mg/l; fibrinogen 608 mg/dl).

A standard radiography of the thorax was taken; this produced a negative result because of pleuro-pulmonary and bony nodal lesions on the thoracic cage.

We sampled exudate for bacterioscopy and culture of KB and for isolation of bacteria and fungi.

At the same time we carried out a biopsy from the edges of the lesion for histological study. While waiting for the results, the patient underwent suitable treatment for the disorders found in the laboratory tests; moreover we carried out treatment with a wide spectrum of antibiotics and drugs against anxiety.

Each day, after lavage with a physiological hydroelectrolytic solution, the ulcerative lesion was medicated, alternating "IntraSite Gel" by Smith + Nephew, which is useful for its cleansing effect, with Actisorb Plus by Johnson&Johnson Ethicon, which has an absorbent action on organic material, exudate and contaminated bacteria and it also has an antimicrobial action; after each medication the basic pain felt by the patient increased and lasted for several hours. During the first six days of treatment the cutaneous lesion spread very slowly in a centrifugal way towards the right and at a speed of about 0.5 cm a day towards the left breast and reached to size of about 9x6 cm; in particular the edges, which the day before had looked separate from the base, the next day looked necrotic and cribrate, secreting pus-like material. However we did not note a further spreading deep in the subcutis; the base, on the right side especially, looked to be cleansed and granular in parts (Fig. 1B).

The medication was sealed daily so it could not be tampered with; this excluded the possibility of pathomimesis.

The cultures from the ulcer were negative and the histological examination of the biopsy showed the presence of a substantial inflammatory infiltrate, which was located in the papillary dermis, particularly around the vessels, and was composed mostly of eosinophiles, histiocytes and lymphocytes; moreover the examination documented vasculitis features and these findings are consistent with the diagnosis of pyoderma gangrenosum, because of the peculiarities of the scene (Figs. 2A and B).

Because of the prevalent association of this lesion with a chronic inflammatory bowel disease, even in the absence of any specific symptomatology, we carried out a colonoscopy which showed edema, hyperaemia and loss of the normal vascular pattern of mucosa of the rectosigmoid tract, which was friable and easily bled when touched, an aspect which is compatible with a case of UC, confirmed by phlogosis of the lamina itself and by the undermining of the glandular structures revealed by the histological examination together with wide areas of superficial erosion.

At this stage, the laboratory investigations were completed with the study of other aspecific indications of phlogosis (alpha-1 glycoprotein serum and alpha-1 antitrypsin serum) and, on the basis of immunomediatic pathogenetic hypothesis of UC and its extraintestinal complications, with the study of the immunological aspect (lymphocyte typing; assay of serum gammaglobulin; complement; circulating immunocomplexes; autoantibodies); in this field, we draw attention to the slight decrease of the C3 fraction of the complement (43 mg/dl), to the presence of circulating immunocomplexes (28 mcgEQ/ml) and to the negative result of

all autoimmune markers. The test for occult blood in the feces proved positive.

The patient was immediately given specific systemic treatment with oral mesalazine (3x800 mg/day) and full dose of oral prednisone (2x50 mg/day, equivalent to 2 mg/kg of body gravity/day); moreover, mesalazine (2 g) and hydrocortisone (125 mg) enemas were also administered twice a day. The support treatment was kept up, associating suitable gastric protection with ranitidine and sucralfate.

For the first 10 days of this treatment, the PG carried on with its rapid, destructive action in a centrifugal direction, continuing to extend almost exclusively towards the left breast and in a cranio-caudal way, until it reached the dimensions of 13.5x9.5 cm; the base presented characteristics of evident cleansing even on the left side and in the area near the border of "advance", and it looked granular. Before taking the almost obligatory decision to carry out immunosuppressive treatment, which is not without complications, a rectosigmoidoscopy was carried out which showed an improvement of the bowel scene, in stark contrast to the worsening of the cutaneous lesion. The results of all laboratory tests were within the normal range. At this point, we decided to leave the specific treatment unchanged and to supplement it on alternate days with infiltrations on the edges of the lesion, especially those of the greatest activity of the disease, with small doses of calcic heparin (5000 UI of calcic heparin were diluted in 10 cc of physiological solution with which 10 perilesional injections were carried out); the aim of this was to exploit the antithrombotic action of the calcic heparin on the phenomena already documented of vasculitis (Fig. 1C).

From the 6th day of antithrombotic topical treatment we noticed the arrest of the centrifugal extension of the cutaneous lesion, whose edges on the 12th day no longer looked mortified and the ulcer base still appeared cleansed and granular; in order to prevent the formation of a hypertrophic scar or a keloid, we proceeded to treat the ulcer base by the adhesive medication of silicone Mepiform by Tendra, which substituted the previous topical treatment. From the 12th day, while the granulation tissue continued to fill the loss of substance, we noticed the initial centripetal growth of the perimetrical epithelium; it formed a rim of translucent-pink pearly colour which, during the following twelve days, characterized by the gradual reduction of the dosage of corticosteroids and the suspension of the treatment with calcic heparin, was going progressively to cover the bloody area (Fig. 1D). Over twelve more days, this was replaced by a delicate, serpiginous and discoloured scar (Fig. 1E).

When the patient was discharged from hospital after 2 months, she was almost completely cured and she was advised to follow a treatment programme under the supervision of her family doctor.

When she went for a follow-up examination after 1 year, the scar had a firm appearance and there was no recurrence of PG or clinical evidence of UC.

Discussion

PG is rarely encountered in clinical practice as an isolated disease; in 75% of cases it is the cutaneous manifestation of an underlying systemic disease (16,24); the latter in half of the cases is represented by a chronic inflammatory bowel disease (2/3 by UC) (3, 43, 51, 59, 62, 70) and 1/3 by Crohn's disease (22, 23, 51, 59, 62) and in the other half of cases by other diseases such as arthritis (65), haematologic diseases (myeloproliferative disorders, Hodgkin's disease, monoclonal

gammopathy usually IgA, multiple myeloma, leukæmia) (27, 44, 50, 53, 58, 68) and some malignant neoplasms (of the breast, colon, prostate, bladder, carcinoma, lymphoma) (35, 36).

The PG incidence in chronic intestinal phlogosis varies from 0.5 to 5% (3, 22, 43, 59) and is equivalent on average to 1% in UC (2, 22, 23, 30, 51, 59).

PG is easily linked to serious, evolutive forms of UC with total involvement of the large bowel, but it has also been described in a small number of subjects with light-to-moderate segmental disease (5, 62, 70). The case we have described, with phlogosis of medium seriousness limited to the sigmoid-rectum area, is included into this category; this demonstrates that there is not always a close correlation between the seriousness and the extension of UC and the development of cutaneous complications.

In more than half of the cases, PG continues in its clinical course on an evident parallelism with the evolutive progress of the intestinal disease: it arises and worsens according to florid stages (initial or relapsing) of UC, at the same time or after the beginning of colonic symptoms (30); the clearing up of PG is linked to the remission of the intestinal illness; it responds to medical treatment of the underlying disorder and it is susceptible to regression after total colectomy and in only 10% of cases after proctocolectomy (20).

On the contrary, in 20% of cases, the cutaneous lesion continues in its clinical course which is independent from the activity of the primary illness (70): it can arise also some years before the UC and appears and persists during the period of quiescence of the latter (30); it responds badly, requiring additional therapy, to direct treatment of the UC, bowel resection included; and it can continue for a long time or develop years after the operation of total colectomy or proctocolectomy (25, 41, 67).

The PG we have described, which appeared in the acute phase of an underlying UC, represents its initial manifestation and is the reason why the patient requested hospitalization; the recognition of PG allowed us, after the suitable investigations of gastroenterology, to reach the diagnosis of colonic inflammation in a sub-clinical phase, since the latter had not been noticed before.

The fact that PG can anticipate the beginning of UC is clear proof of the theory that considers the two manifestations, colonic and extracolonic, to be different clinical expressions of a single systemic disease, the pathogenic cause of which acts independently both on the large intestine, the main organ that is targeted, and on other and tissues; the absence of a correlation between the seriousness and the extension of UC and the cutaneous complication testifies the same hypothesis. On the other hand, to give support to the theory that the skin disorder is secondary to the bowel disease, we can

refer to the clinical data which marks its regression on the occasion of the improvement of the underlying pathology and the beneficial effect that total colectomy and proctocolectomy have on it. Therefore, the relationship between UC and associated PG is still unknown, as the exact etiological and pathogenetic mechanism of the latter has not been demonstrated and remains an enigma.

Although the term "pyoderma" implies a bacterial infection, this is not the cause of the lesion, which is primarily sterile, and the possible discovery of microbial colonization does not have any etiological value since it is usually a case of suprainfection.

PG, on the contrary, can be attributed to a bad regulation of the immunity of the organism with phenomena on multiple areas of dangerous responsiveness and of autoimmunity and to a bad functioning of polymorphonuclear leucocytes with defects in phagocytosis and chemotaxis (21, 45, 61).

Particular attention must be paid to the probable role of mast cells activated and of the release of powerful inflammatory molecules contained in them and to the suggestive but not well-defined role of the large amounts of immunocomplexes circulating which deposit themselves in the walls of the skin vessels, favouring the onset of vasculitis (9, 10, 41, 45, 52).

A common mediator involves immunopathologic causative phenomena of PG and UC; this is represented by a colonic antigen, if it is autologous, or by an alimentary, bacterial, chemical kind of antigen, if it is heterologous, because of an altered state of permeability of the bowel wall by primary phlogosis (31, 42, 66).

The onset of PG on the site of an previous cutaneous trauma in 10-27% of cases (15, 38, 55), even that small of endovenous injection, puts it into a category of aspecific cutaneous hyperergia.

The single case of PG that we examined does not allow us to enter in depth into the merits of the discussion relative to the etiology and pathogenesis of the disease; we have limited ourselves to referring to the hypotheses which emerged from the literature and we have avoided expressing the conclusions that we ourselves came to during the examination, since we could not back them up by adequate experience.

The extracolonic complication of UC can be seen especially in young, female patients (3), like the one we observed, and can afflict any area of the skin, though lesions of the lower limbs prevail (57), especially in the pretibial region (54); lesions are rarely found on the head and neck (63), the penile and scrotal skin (60), the peristomal area (8, 47, 49) and the area around laparotomies (17, 34). As far as we know, there are no other cases in the literature of PG situated in the space between the breasts, as in the case we have described.

The diagnosis of PG is based, as in our case, principally on the morphological peculiar characteristics, in a masterly fashion set out in 1930 by Brunsting (7).

The initial cutaneous lesion is represented by an dermic erythematous nodule; it is hard, elastic, painful (papula) and, gradually, increases in size and in the central part tends towards colliquative necrosis with the formation of a collection of non-septic puruloid material, containing few polymorphonuclear cells and no bacteria and covered by a thin bluish epidermic membrane (pustule). In a few days the collected material may drain away of its own accord and in this way an ulceration develops; with the progression of necrotic phenomena and with almost inevitable secondary bacterial colonization, it spreads in depth in the subcutis and in a centrifugal sense towards the surrounding areas at the speed of 1-2 cm/24 hours, leaving the skin at first detached from the deep levels but then that too is involved in the necrosis. The sluggish, terebrant ulceration appears as an irregular, jagged form; it is up to 30 cm in size and is quite painful; it has undermining, cribrate edges with several openings which drain material that is puruloid or frankly purulent; the edges violescent for the passive hyperaemia give rise, around the ulceration, 5-8 mm in width, to a blue, shining halo and overlap a reddish base, sometimes covered with necrotic, whitish tissue; a area of erythema spreads like an areola over the surrounding normal skin.

In the case we have described, we did not encounter toxicity, septicaemia with high fever or cutaneous lesions associated with diverse typologies (nodose erythema, vesiculo-pustular lesions), which are often seen in PG.

There are no pathognomonic laboratory data of the cutaneous manifestation of UC which we have already mentioned and the only positive results concern the haematochemical ratios of the underlying disease, including those immunopathological ones of dubious interpretation.

The histopathological picture of PG is not specific (66) and is only useful in order to exclude other possible pathologies. It is marked by a massive dermal inflammatory infiltration, especially perivascular, composed of polymorphonuclear leucocytes, histiocytes and, at a later stage, lymphocytes; a vasculitis process is present.

The histological investigation of the edges of the ulcerative cutaneous lesion we have illustrated shows up a substantial presence of acidocytes, rather than the ordinary detection of neutrophiles in the dermal infiltration of PG, included among neutrofile dermatosis for this reason (4, 28). However, this histological finding of ours is part of the various aspects seen in this disease.

A differential diagnosis must consider the cutaneous ulcerations in the course of pathomimesis, those of necrotizing vasculitis from hypersensibility (37) and those that are bacterial, mycotic, mycobacterial, viral and parasitic; venous and arterial ulcers situated in the lower limbs must not be neglected.

The spontaneous healing of PG, a rare event, or its healing following treatment takes place very slowly with the cessation of the inflammatory process, the beginning of reepithelization from the edges to the centre and the resulting in a serpiginous scar with atrophic, iper- or ipo-pigmented skin (43, 57).

In 1/3 of cases, the cutaneous lesion recurs in the same place or in another place (5, 43) and the smallest trauma may be responsible for the relapse.

The treatment of PG is empiric and not codified.

Pharmacological treatment is aimed at controlling the underlying UC and its remission which, in most cases, is responsible for the improvement or the healing of the cutaneous ulcer (45, 70), although we cannot exclude some favourable effect of treatment directly on the skin disorder; however, we cannot quantify this with accuracy. The treatment uses salazopyrine (43) or mesalazine and/or corticosteroids (prednisone, prednisolone, methylprednisolone) (6, 18), all on full dosage.

In PG that is resistant to the common treatment of underlying UC and also in order to speed up the healing, topical treatment is worth trying.

Intralesional injections (in the edges of the ulcer) of corticosteroids and likewise packs of water solution with 2% disodium cromoglycate (11, 39) seem to produce good results, but not always (19, 29); the therapeutic action of this substance is based on the inhibition of the liberation of chemical mediators by the mast cells and the rise of the limit of reactivity.

As a support to specific treatment, systemic antibiotics doubtlessly are important in the definitive remission of the cutaneous lesion (minocycline; rifampicin (13, 68) and topical (hydrogen peroxide, benzoyl peroxide (48), with their contrasting action on its secondary infection; also of relevance are all the other local medical means concerning the wound bed preparation which, by keeping the necrosis away from the ulceration with an action of debridement and stimulating its granulation and reepithelization, actually favour the regeneration and tissue repair and therefore create the best healing conditions.

Good results have been noted with the use of hyperbaric oxygen (69).

In the case of resistance of PG to the conventional treatment of UC, we must not forget the use of immunosuppressive (azathioprine, 6-mercaptopurine, metotrexate, cyclophosphamide, chlorambucil, cyclosporine A) (6, 9, 14, 40, 46) and anti-leprosy drugs, despite the fact that we are uncertain about their modality of

action on the skin disorder and the fact that they are not always efficacious (clofazimine, dapsone) (32, 33, 48, 64).

If non-invasive treatment of UC does not work on the evolution of PG or if it persists or it becomes worse it recurs, the efficacy of total colectomy has been pointed out since it improves or totally clears up the cutaneous lesion; this was also the experience of Goligher (20) who, however, as we have already mentioned, in 10% of cases, saw the persistence of PG as long as the rectal stump was left in place; however, after it was taken away, PG suddenly disappeared. The surgical excision of the intestine would offer, therefore, the excellent but drastic prospect of dominating the cutaneous disorder (30).

In the case of PG we studied, which proved to be resistant to the usual medical treatment of the underlying UC, we wanted to avoid the use of immunosuppressive drugs with their serious complications and especially the highly debilitating total colectomy or the proctocolectomy, considering also the endoscopic improvement of the intestinal situation. Therefore, instead of these and alongside conventional treatment, we decided to use infiltrations on the "active" edges of the lesion of small doses of calcic heparin (5000 UI of calcic heparin were diluted in 10 cc of physiological

solution with which about 10 perilesional injections were carried out on alternate days); this was done in an effort to control, by exploiting the antithrombotic effect of the drug, those phenomena of vasculitis histologically discovered on the edges of the skin disorder, in the onset of which they have certainly physiopathological importance.

The fact that topical antithrombotic treatment was successful in the single case of PG associated with UC that we treated does not allow us to draw any definite conclusions about its effectiveness in the healing of an ulcerative cutaneous lesion. We feel that, up to now, it can and must represent only an additional medical therapy to be used side by side with current treatment of PG; however, it must be given due consideration in all cases in which PG is resistant to the usual medical treatment of UC, since although the skin disease, even if may predominate in the general clinical situation because of its destructive qualities, it cannot constitute an autonomous indication for immunosuppressive drugs or for proctocolectomy, which should be resorted to only if the conditions of the colon, after careful examination, impose it, since the aforesaid treatments do not lead to an unequivocal, definitive cure because their effect cannot be predicted with precision (25, 41, 67).

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