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Treatment of granulomatous disorders of the nose and paranasal sinuses

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SUMMARY

The granulomatous disorders discussed in this review are Wegener's granulomatosis (WG), lymphomatoid granulomatosis (polymorphic reticulosis) and "idiopathic midline granuloma". The treatment of choice of WG is combined therapy with corticosteroids and cyclophosphamide. Severely ill patients may be treated with intravenous bolus infusions of cyclophosphamide. Otherwise oral administration is used. Therapy must be adjusted according to leucocyte and thrombocyte counts. After clinical remission cyclophosphamide must be continued for at least a year under hydration sufficient to cause nycturia in order to protect the bladder mucosa. Corticosteroids can be withdrawn 9–10 months after clinical remission. Relapse of WG can be identified by clinical and laboratory (ESR, CRP, HB, urinary sediment) findings, including detection of anti-neutrophil cytoplasm antibodies (ANCA). Alternate treatment with azathioprine or trimethoprim/sulfamethoxazole may be used in patients with localized or smoldering disease. Furthermore trimethoprim/sulfamethoxazole may be used as adjunctive treatment. Lymphomatoid granulomatosis appears to be a T-cell lymphoma and should be treated aggressively with combination cytotoxic therapy and irradiation of localized manifestations. "Idiopathic midline granuloma" does not seem to exist but appears to be either WG or lymphomatoid granulomatosis when repeated biopsies are examined with monoclonal antibodies and/or serum examined for ANCA.

INTRODUCTION

The present review deals with the treatment of presumed non-infectious, autoimmune or malignant granulomatous lesions, which may appear localized to the nose and paranasal sinuses comprising Wegener's granulomatosis (WG),

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lymphomatoid granulomatosis (polymorphic reticulosis) and "idiopathic midline granuloma". The clinical and histological differentiation and pitfalls have been outlined in previous contributions (Wegener, 1939; Carrington and Liebow, 1966; Liebow et al., 1972).

TREATMENT OF WEGENER'S GRANULOMATOSIS

Several possibilities have been described for treating WG (Table 1). Untreated, WG runs a lethal course with an 80% mortality by the end of the first year following diagnosis and 93% in two years (Walton, 1958). The prevailing causes of death were renal (55%) and pulmonary failure (21%). Corticosteroids seemed to improve the survival of patients to some extent, but the disease usually remained fatal with an average survival time of 12.5 months (Beidleman, 1963; Reza et al., 1975). The main effect of steroids was to obviate the facial deformities and to prevent exsanguination haemorrhage. As patients with end stage renal failure may survive for years on chronic maintenance dialysis, the survival expectancy of individual patients treated only with corticosteroids may – based on personal experience – be better than hitherto believed. Reports on local irradiation suggested a transient response only (Wegener's granulomatosis. Clinicopathological Conference, 1963). Not until the introduction of cytotoxic immunosuppressive therapy, particularly cyclophosphamide (CY), has WG become a potentially curable disease. Nitrogen mustard, methotrexate, chlorambucil and azathiprine have been applied with some success (McIlvanie, 1966; Bouroncle et al., 1967; Hollander and Manning, 1967; Aldo et al., 1970), but only CY seems to decisively change the long-term prognosis of the disease, although classical, controlled clinical trials have not been performed (Novak and Pearson, 1971; Fauci et al., 1983).

Table 1. Various therapeutic modalities used in the treatment of Wegener's granulomatosis.

glucocorticoids	
cytotoxic agents:	cyclophosphamide azathioprine chlorambucil nitrogen mustard methotrexate
antimicrobial agents:	trimethoprim-sulfamethoxazole
cyclosporin A	
plasmapheresis	
local irradiation	

Cyclophosphamide

Today there is unaminous evidence that the generalized active form of WG should be treated with CY. The generalized form of WG appears as an involvement of various organs, usually the nose, the lungs and the kidneys, accompanied by general symptoms like fever, weight loss, general malaise, arthralgia, myalgia and anaemia (McDonald and DeRemee, 1983). The prospective treatment schedule outlined by Fauci and coworkers (1983) depends on whether the patient, on admission, is critically ill or not. Critically ill patients should receive CY 5–10 mg/kg intravenously for 2–3 days under hydration. We have adopted a slightly different schedule applying CY as a bolus administration of 1 g (or less depending on the renal function) for one day under hydration and under cover of an uroprotector, MESNA, which seems to neutralize the toxic activity of acrolein, an metabolite of CY, on the bladder mucosa (Bryant et al., 1980). The bolus infusion of CY is repeated twice every 14–28 days after the preceeding dose depending on white blood cell and platelet count. Thereupon CY is given via the oral route, usually 1–3 mg/kg/day depending again on the white blood cell count. It is a prerequisite for the oral intake of CY that adequate diuresis is obtained leading to nycturia (1–2 times).

Patients without kidney involvement may be treated initially with oral CY (1–3 mg/kg/day). The dosage of CY should be carefully adjusted to maintain a total leucocyte count between 3500–5000/mm^3 and a total neutrophil count of 1000–1500/mm^3, thus preventing opportunistic (especially pulmonary) infections, which are frequently the cause of death in excessively immunosuppressed patients.

Steroids

Since there is no effect of CY before the 5th day and the therapeutic efficiency is not achieved until the first month after administration, concomitant application of steroids is mandatory at the beginning of therapy. Moreover, the addition of corticosteroids may be favourable due to its myelostimulating properties (Dale et al., 1975). Depending on the state of the patient prednisolone may be given either as a bolus of 7–15 mg/kg/day for three days, then gradually tapered off to 0.5 mg/kg/day within one month, or as a 1 mg/kg/day dose for 2–4 weeks, until the immunosuppressive effect of CY is seen as reflected by the leucocyte count (Harrison et al., 1980; Fauci et al., 1983). In both instances the dose is then converted to an alternate day treatment with 1 mg/kg every second day over 1–2 months. With this alternate day regimen the dose is then gradually tapered off to 20 mg/every second day or less over six months to one year according to the individual response to therapy. Some doubt, however, exists concerning the effect of steroids in the long-term treatment of WG, as the usual doses of steroids in these instances are relatively low. In general, the effect of administration of steroids is not sufficiently investigated. Until now, no one has examined whether higher

initial steroid doses, e.g. bolus infusion, and/or prolonged administration of higher steroid doses may be as effective as CY in the long-term prognosis of WG, especially if combined with other treatment modalities than CY.

Terminating therapy

Too early reduction of therapy may trigger relapse (Figure 1). If signs of relapse are observed, the dosage of prednisolone and/or CY should be raised until improvement is evident. After complete remission CY should be continued for at least one year. Prednisolone should be tapered off first, usually 2–3 months

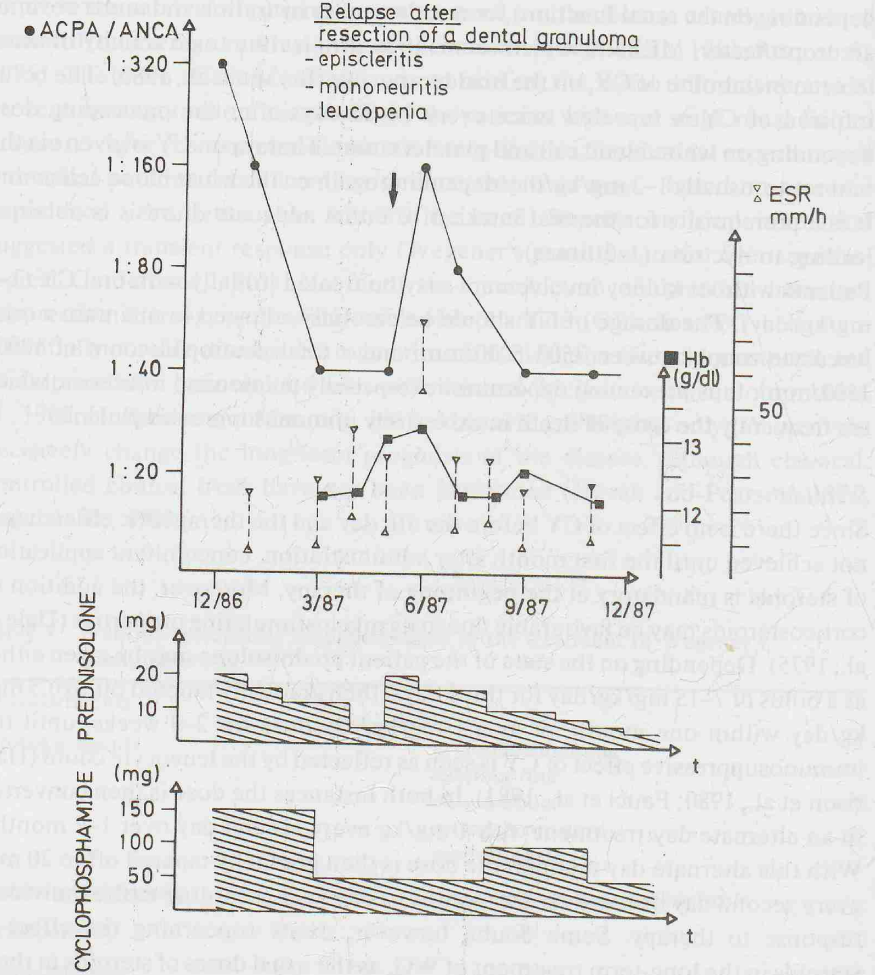

Figure 1. Relapse of Wegener's granulomatosis after resection of a dental granuloma. Due to leucopenia, remission could only be achieved by increasing the dosage of steroids.

before termination of CY. According to Fauci et al. (1983) the ESR, as an indicator of disease activity, should be normal for at least one year before the patient can be taken off CY. However, ESR may not always be reliable as a disease marker, and it has been suggested that C reactive protein (CRP) be used instead or additionally (Hind et al., 1984). The newly identified anti-neutrophil cytoplasm antibodies (ANCA/ACPA) may not be helpful in this situation as they may become negative despite persisting disease activity or may persist despite of no clinical signs of disease activity (van der Woude et al., 1985). However, in most cases, ANCA follows disease activity, and may be used to differentiate between relapses and superinfections.

Side effects of cyclophosphamide therapy

The appliction of cytotoxic drugs in non-neoplastic diseases is still a matter of concern due to the potential, serious side effects. Only a few patients cannot tolerate CY because of haematological, urological or gonadal problems (Gershwin et al., 1974; Warne et al., 1974). In such situations azathioprine may be used as a substitute, but it has to be taken into consideration that several patients fail to achieve remission if azathioprine is used as the first drug, CY being the drug of choice for induction of remission. However, with the long-term use of CY the risk of malignancies might exceed 5%. Three quarters of those being affected by malignancies suffer from leukemia, lymphoma or bladder cancer (Green et al., 1986). The total dose of CY in patients with malignancies ranged between 12 and 170 g (Puri and Campbell, 1977). Whereas there seems to be a correlation between the development of leukemia and the duration of therapy this does not appear to be the case for the other malignancies. Stillwell et al. (1988) showed that there is a 9 to 45-fold increased risk of bladder carcinoma following CY therapy. Accordingly, several groups have changed their treatment protocols in order to reduce the total dose of CY, but controlled studies are still lacking. Some keep to intravenous bolus administration of CY on a monthly or bimonthly basis, thus considerably lowering the total dose (Gross et al., 1987), while others switch to azathioprine after a 12 weeks course with CY taking the risk of relapse in some patients as shown in Figure 2 (Pinching et al., 1983).

Other treatment modalities

In order to replace CY or reduce the need for CY treatment several other possibilities have been investigated. Based on a presumed pathogenetic role of circulating immune complexes plasmapheresis has been suggested as initial treatment, but the pathogenetic role of circulating immune complexes is uncertain and an additional beneficial effect of plasmapheresis has not yet been demonstrated (Pinching et al., 1980). At present this procedure may therefore be confined to patients in need of hemodialysis due to acute renal failure (Pinching et al., 1983; Lockwood, personal communication).

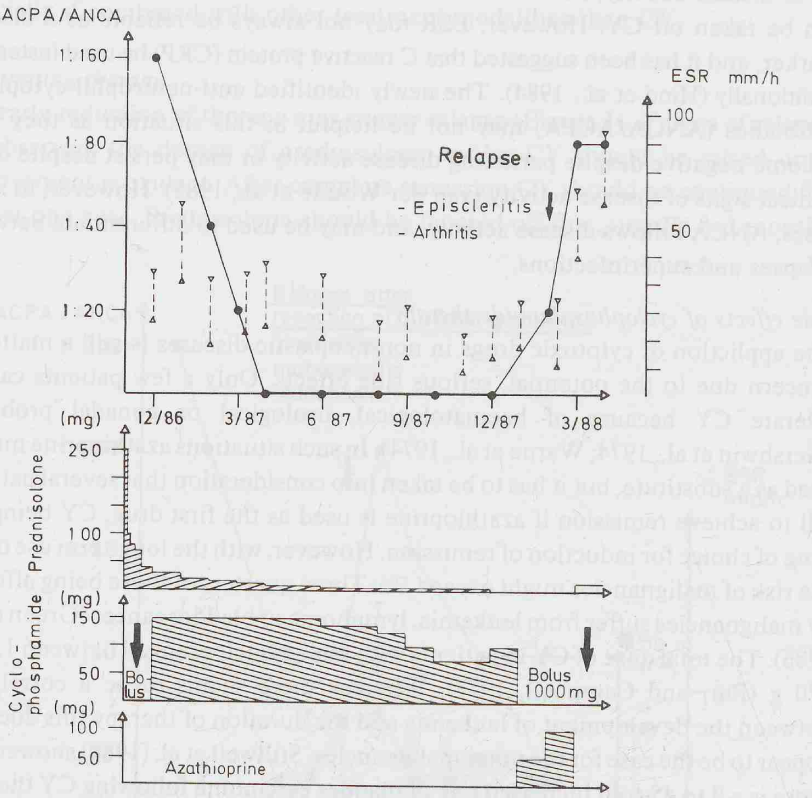

Figure 2. Relapse of Wegener's granulomatosis after replacement of cyclophosphamide by azathioprine. Remission was achieved by repeated cyclophosphamide bolus administration.

As also discussed above, azathioprine may in certain cases be an alternative to CY, especially as azathioprine is far less toxic. Azathioprine therapy appears particularly preferable in younger patients, although some of these patients manifest with a severe form of disease. A careful observation of these patients is therefore mandatory and a primary regimen with azathioprine and steroids is only advisable for patients with a smoldering course of disease.

The supportive treatment of superinfections in the upper respiratory tract, usually caused by staphylococci, is essential, since infections are known to trigger relapses in WG (Pinching et al., 1980). Treatment of WG with antimicrobial agents (especially trimethoprim-sulfamethoxazole (TMZ)) may improve the clinical course of WG by itself (DeRemee et al., 1985; DeRemee, in press).

A daily regimen of TMZ used as the only drug may be justified as one double strength tablet for months or even a year in localized forms under close observation, as the disease remains active in some patients despite TMZ treatment. TMZ monotherapy might also be applied to patients with a more indolent course of the disease, but TMZ is mainly recommended as an adjunctive drug to the CY/prednisolone combination, leading to impressive clinical improvement in certain patients (Andrassy et al., 1987; West et al., 1987). TMZ may act either by elimination of the offending microbe, as the presence of granulomatous inflammation in WG may suggest an infectious cause, or TMZ could have an effect as an immunosuppressive drug due to its folic acid antagonism.

The effect of Cyclosporin A has been described in a few case reports. A beneficial effect has only been described by Gremmel et al. (1988), whereas our own experience and that of others has been negative.

As many more cases of WG are now being detected with the aid of the ANCA/ACPA test, the possibility of performing clinically controlled studies has increased considerably. Thus the answer to several of the questions concerning the optimal treatment of WG may be solved within the near future.

LOCALIZED WEGENER'S GRANULOMATOSIS

Although there is a general agreement on the treatment of generalized WG, some disputes exist about the therapy of the localized forms. Such forms usually represent an early stage of the disease. In various studies including our own the involvement of the nose and paranasal sinuses was the most frequent initial and localized manifestation of WG. Since the disease is often overlooked at this stage, as the histological proof – even in cases where WG is suspected – unfortunately is only obtained in 1/3 of the patients, therapy is often seriously delayed. By means of the new test for ANCA/ACPA the chance of early identification has considerably increased as ANCA/ACPA are also present in the early stages of the disease (Van der Woude et al., 1985; Andrassy et al., 1989). In the early stages of WG, one of the less toxic therapeutic regimens discussed above may be attempted as the development of the disease can now be followed and controlled. Since kidney involvement is the most serious and also a sensitive indicator of generalization of the disease, frequent examinations of the urine are recommended. If urinary tract infections are excluded the onset of haematuria, proteinuria, leucocyturia and the detection of erythrocyte and granular casts indicates kidney involvement and thus generalization of the disease. In such cases, treatment with CY and prednisolone must be installed immediately.

OTHER FORMS OF "MIDLINE GRANULOMA"

Localized WG, as discussed above, is one form of "midline granuloma" (Editorial, 1977). Another distinct disease entity is polymorphic reticulosis, originally

described as a lymphoma (Eichel et al., 1966), which appears histopathologically to be identical to lymphomatoid granulomatosis (LYG) (DeRemee et al., 1978). In the seventies, LYG was presumed to be of autoimmune nature and a treatment regimen close to that for WG was reported with favourable results by Fauci and coworkers (1982). However, with the advent of monoclonal antibody characterization of the cellular components of the lesions it has now been substantiated, that LYG is indeed a T-cell lymphoma (Nichols et al., 1982), indicating that LYG – and thus polymorphic reticulosis – should be treated with an intravenous, combined cytotoxic regimen. Although a limited series from the NIH (Fauci et al., 1976) using local irradiation in the treatment of midline granuloma – including patients with WG as well as LYG – revealed favourable results, local irradiation should only be used as adjunctive therapy.

Whether "idiopathic midline granuloma" exists as a separate disease entity has been discussed widely (Editorial, 1977). With the use of monoclonal antibody characterization of lesions and detection of ANCA/ACPA in serum it appears that the earlier problems of distinguishing between WG, LYG and "idiopathic midline granuloma" may disappear, leaving us with only two distinct diseases, WG and LYG, with individual treatment regimens as discussed above.

CONCLUSION

WG is the most significant of the granulomatous diseases discussed in the present review. The treatment of choice for WG – localized as well as generalized – is cyclophosphamide and prednisolone, with the possibility of initial treatment of localized forms with less toxic regimens under close control of disease activity.

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