Case study

Chronic granulomatous disease as a risk factor for autoimmune disease

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Chronic granulomatous disease (CGD) is characterized by recurrent infections and granuloma formation. In addition, we have observed a number of diverse autoimmune conditions in our CGD population, suggesting that patients with CGD are at an elevated risk for development of autoimmune disorders. In this report, we describe antiphospholipid syndrome, recurrent pericardial effusion, juvenile idiopathic arthritis, IgA nephropathy, cutaneous lupus erythematosus, and autoimmune pulmonary disease in the setting of CGD. The presence and type of autoimmune disease have important treatment implications for patients with CGD. (J Allergy Clin Immunol 2008;122:1097-103.)

Key words: *Chronic granulomatous disease, autoimmune, antiphospholipid syndrome, IgA nephropathy, lupus, juvenile idiopathic nephropathy*

Abbreviations used
ANA: Antinuclear antibody
aPL: Antiphospholipid syndrome
CGD: Chronic granulomatous disease
CT: Computed tomography
JIA: Juvenile idiopathic arthritis
LE: Lupus erythematosus
NIH: National Institutes of Health
PID: Primary immunodeficiency
RF: Rheumatoid factor

Chronic granulomatous disease (CGD) is a primary immunodeficiency (PID) resulting from a defect in the multicomponent nicotinamide adenine dinucleotide phosphate oxidase complex, which is responsible for production of bactericidal reactive oxygen species in phagocytes. As a result, patients with CGD are at increased susceptibility to certain catalase-positive bacteria and fungi, and *Aspergillus* species.[1] The primary clinical features of CGD are recurrent infections and granuloma formation. However, reports of sarcoidosis,[2] juvenile idiopathic arthritis (JIA),[3] IgA nephropathy,[4] pericardial effusion,[5] and severe Crohn-like inflammatory bowel disease[6] suggest that the breadth of altered immune regulation extends beyond recurrent infections and granulomas. We propose, in addition, that patients with CGD are at significant risk for development of autoimmune disease (AI), and provide a series of case reports and a review of the literature to support that hypothesis. Specifically, we report here the following AIs in our patients with CGD: antiphospholipid syndrome (aPL), JIA, IgA nephropathy; steroid-responsive recurrent pericardial effusions, cutaneous lupus erythematosus (LE), and a patient with geographic pulmonary lesions, a finding we have observed in 4 other patients with CGD.

CASE PRESENTATIONS

Case 1: aPL

A 14.5-year-old white boy was diagnosed with X-linked (gp91^{phox}-deficient) CGD after the development of *Serratia marcescens* abscesses of his neck and mesentery at 3 years of age. Long-term prophylaxis consisting of trimethoprim-sulfamethoxazole, itraconazole, and IFN-γ was commenced. Of interest, his mother (a CGD carrier) and maternal aunt (not a carrier) were both diagnosed with discoid lupus. At 10 years, he developed cellulitis of his arm after a minor skin abrasion. Treatment with intravenous antibiotics was complicated by venous thrombosis in his affected arm, which was treated with a 3-month course of warfarin. At age 14 years, he described acute swelling, pain, and redness of the left thigh, with no other associated symptoms, fever, or history of trauma. His laboratory tests were unremarkable other than an erythrocyte sedimentation rate (ESR) of 50 mm/h (National Institutes of Health [NIH] range, 0-25 mm/h). Doppler ultrasound revealed a left femoral deep venous thrombosis, and he was treated initially with heparin, followed by warfarin anticoagulation. Four months later, he was seen at our clinic with fever, bullous otitis media, and severe headaches. On physical examination, he was normotensive, and his fundoscopy was unremarkable. He had a leukocytosis with a total white blood cell count of 16×10^9/L (neutrophils 81.4%) and ESR of 101 mm/h. Computed tomography (CT) imaging of his head at this time was unremarkable. He was treated with levofloxacin for bullous otitis media and maintained on warfarin 3.5 mg daily with a goal International Normalized Ratio

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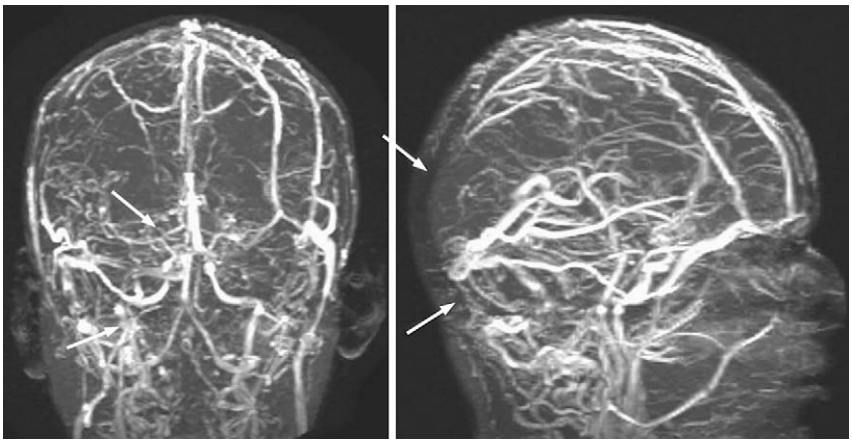

FIG 1. A magnetic resonance angiogram of the brain revealing filling defects *(white arrows)* caused by extensive intracerebral venous thrombosis.

of 3. His frontal and ocular headaches persisted, and ophthalmologic examination 1 month later revealed flame hemorrhages and papilledema caused by raised intracranial pressure. A venous magnetic resonance angiography revealed extensive old cerebral sinus venous thrombosis involving the right sigmoid, transverse, and superior sagittal sinuses (Fig 1). The patient's headaches resolved, and he resumed normal activities. He returned 2 months later with extensive new clots in the left common femoral, superficial femoral, popliteal veins, and a superficial vein in the left calf resulting in near-complete veno-occlusion. Extensive hematologic evaluation ruled out an underlying hereditary hypercoagulability, including the absence of anticlotting factor antibodies. Negative evaluations included activated protein C resistance, protein S and protein C deficiency, antithrombin III deficiency, prothrombin G20210A mutation, methylenetetrahydrofolate reductase C677T polymorphism, homocysteinemia, and β2-glycoprotein antibodies. Screening was also negative for rheumatoid factor and the following autoantibodies: anticardiolipin antibodies (IgG and IgM), anti–extractable nuclear antibodies (ENA), anti–double-stranded DNA (dsDNA), cytoplasmic-antineutrophil cytoplasmic antibody (c-ANCA), and perinuclear-antineutrophil cytoplasmic antibody (p-ANCA). However, lupus anticoagulant, not uncommonly detected in asymptomatic patients with CGD, was present, and antinuclear antibody (ANA) was positive. A trial of oral prednisone at 0.5 mg/kg/d (30 mg/d) was commenced. Within 24 hours, his leg swelling and pain improved dramatically. His prednisone dose was slowly tapered over several weeks with recurrence of symptoms (leg swelling, erythema, and pain on ambulation) at a dose of 5 mg daily. His prednisone dose was increased to 15 mg daily with resolution of his symptoms. Repeat evaluation of his autoantibodies and inflammatory markers revealed elevated ESR and C-reactive protein (101 mm/h and 13.6 mg/dL), and again, positive lupus anticoagulant. Thus he fulfilled the recently revised criteria for the diagnosis of aPL (2006 International Consensus Statement on an update of the classification criteria for definite aPL).[7] Methotrexate was instituted as a steroid-sparing agent and has allowed tapering of prednisone to 7.5 mg (current weight, 57.8 kg) on alternate days while continuing warfarin 3.0 mg daily (INR, 2.6) without further progression of thrombosis to date. Follow-up imaging examinations have demonstrated slow resolution of the thromboses with venous recanalization in the head and leg.

Case 2: Recurrent extensive pericardial effusion

Patient 2 is a 13-year-old white boy diagnosed with X-linked CGD in infancy. Trimethoprim-sulfamethoxazole and itraconazole prophylaxis without IFN-γ was commenced on diagnosis. At 9 months of age, he presented with respiratory distress without fevers or any obvious sites of infection. A significant pericardial effusion was identified, and pericardiocentesis was performed for both diagnostic and therapeutic purposes. No etiology for the effusion could be determined, and the patient was given an empiric trial of prednisone, which was effective and then tapered over several weeks. However, the pericardial effusion recurred approximately every 6 months over the next 3 years with similar workup, treatment, and outcome. At age 7 years, he developed pulmonary *Cryptococcus*, which responded to fluconazole. A month later, he returned with fevers, malaise, and dysphagia. His laboratory parameters (white blood cell count; electrolytes; liver, kidney, and thyroid function tests) were unremarkable except for an elevated ESR (108 mm/h) and CRP (6.7 mg/dL). A chest radiograph showed an enlarged cardiac shadow, and a large pericardial effusion was confirmed by chest CT (Fig 2). An echocardiogram revealed normal cardiac structure and function. Bacterial, fungal, and viral cultures from the effusion fluid obtained from pericardiocenteses were also negative, as were cultures from his blood. The pericardial effusion resolved promptly on recommencement of methylprednisolone over the next 5 days, and empiric antibiotics were discontinued (all cultures were negative). The patient was discharged a week later with resolution of the effusion by echocardiogram and sent home on a tapering dose of oral prednisone. On low-dose maintenance alternate-day prednisone, he has not had any recurrences to date over a period of more than 4 years of follow-up.

Case 3: IgA nephropathy

Patient 3 is a 17-year-old white boy with X-linked CGD diagnosed at 3 years of age. Prophylaxis included trimethoprim-sulfamethoxazole and itraconazole without IFN-γ. His past history is significant for recurrent cystic acne, *Staphylococcus aureus* liver abscesses, lymphadenitis, and multiple pulmonary infections (including *Aspergillus* and *Nocardia*). At age 13 years, during an admission to the NIH for a fungal pneumonia (treated with voriconazole), isolated hematuria and trace proteinuria

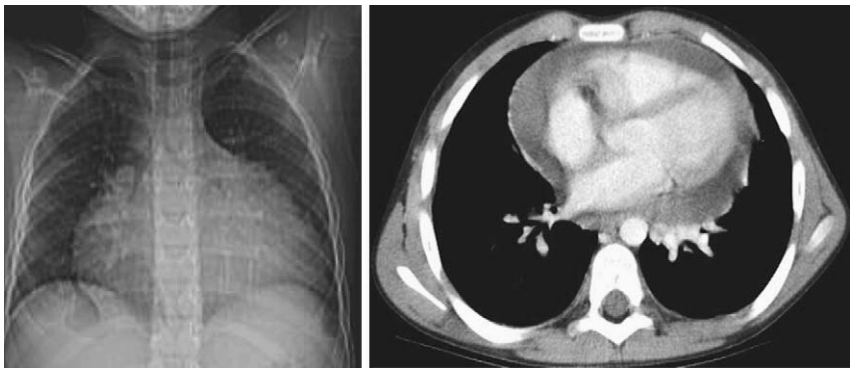

FIG 2. An enlarged cardiac silhouette on chest X-ray caused by massive pericardial effusion confirmed on chest CT.

were noted with a serum creatinine of 1.0 mg/dL. Significant proteinuria, 2+ blood cells in the urine, and granular and hyaline casts persisted and over the next month. His creatinine (which had a historical baseline of 0.8 mg/dL) increased to 1.9 mg/dL, and he became oliguric. An extensive renal assessment was performed to evaluate for postinfectious glomerulonephritis, IgA nephropathy, vasculitis, or connective tissue disorders. ANA, anti-ENA, anti-dsDNA, p-ANCA, c-ANCA, antimyeloperoxidase, antiproteinase-3, rheumatoid factor (RF), and serum complements C3 and C4 were all within normal limits. Urinary excretion of calcium and phosphorus were within normal range. A renal biopsy revealed a focal segmental proliferative and necrotizing crescentic glomerulonephritis and mesangial IgA deposits on immunofluorescence consistent with IgA nephropathy. He was treated with prednisone 30 mg twice daily, and his creatinine rapidly improved to 1.1 mg/dL over the next week, allowing a slow taper of oral prednisone. Two months later, his creatinine had stabilized at his baseline level of 0.8 mg/dL. Over the following years, his renal function has been normal on continued low-dose, alternate-day oral prednisone 2.5 mg. We have in our cohort another patient with similar steroid-responsive renal impairment caused by IgA nephropathy. In both patients, there was no family history of autoimmune diseases.

Case 4: JIA

Patient 4 is a 26-year-old white woman diagnosed with $p47^{phox}$-deficient CGD at birth. Her early course was remarkable for recurrent sinusitis, otitis media, and pulmonary infections. At age 15 years, she developed arthralgias of her elbows and hands, which progressed to bilateral involvement of her elbows, knees, and hands. Physical examination revealed erythematous macules and papules on the arms and forehead, bilateral swelling of the metacarpal and proximal interphalangeal joints, and numerous rheumatoid nodules. ANA, ENA, and dsDNA were unremarkable, as were cultures of blood and synovial fluid, except for an elevated RF (97 IU/mL). A biopsy of the joint showed perivascular synovitis without lymphoid aggregates. Radiographs of the hands, wrists, elbows, feet, and ankles revealed mild subchondral lucency at the right third metacarpal head but no joint space loss or bone destruction. She was treated with nonsteroidal anti-inflammatory medications and minocycline with only transient improvement. Etanercept 25 mg subcutaneously biweekly was commenced, which led to resolution of her symptoms. When etanercept was discontinued for a poorly healing wound, her symptoms recurred. Treatment with naproxen and tramadol gave only transient improvement, so etanercept was reinstituted with good response. This case is representative of 1 other patient with JIA in our cohort, who required gold injections in addition to hydroxychloroquine and prednisone for maintenance of disease remission.

Case 5: Cutaneous LE

Patient 5 is a 21-year old white man diagnosed with X-linked CGD at 18 months of age. Long-term antibiotic and antifungal prophylaxis as well as IFN-γ were initiated. At age 12 years, he was diagnosed with cutaneous LE after development of a rash on his chest. His rash improved with residual scarring after treatment with topical corticosteroid therapy. Of note, his mother, a CGD carrier, was diagnosed with cutaneous LE. At the time of this presentation, he reported a 2-month history of large annular, erythematous plaques on the chest, malar rash (Fig 3), and erythematous plaques on the scalp with associated alopecia. He denied symptoms of other organ involvement, significant diarrhea, or abdominal pain. Other than the rash, his physical examination was unremarkable. Laboratory evaluation revealed negative antibodies to cardiolipin, dsDNA, ENA, ANA, anti-Smith, antihistone, RF, anti-Sjogren syndrome A antibody (anti-Ro) and anti-Sjogren syndrome B antibody (anti-La), and lupus anticoagulant. His ESR was not elevated. A diagnostic skin biopsy again confirmed cutaneous LE. After a week of clobetasol ointment 0.05% without significant improvement, a tapering dose of oral prednisone was commenced, which resulted in marked improvement. He continues on low-dose, alternate-day, 5-mg-daily prednisone.

Case 6: Recurrent aphthous stomatitis and pulmonary infiltrates

Patient 6 is a 14-year-old white boy with $p47^{phox}$-deficient CGD diagnosed at 16 months of age, following a history of lymphadenitis and staphylococcal skin abscesses. Standard CGD prophylaxis consisting of trimethoprim-sulfamethaxozole, itraconazole, and IFN-γ was commenced. He had a history of multiple dermatologic problems, including photosensitivity (face, arms, trunk), eczematous skin lesions, guttate psoriasis, and impetigo. Photosensitivity symptoms did not improve after cessation of trimethoprim-sulfamethoxazole, a known photosensitizer. At age 10 years, he developed persistent cheilitis

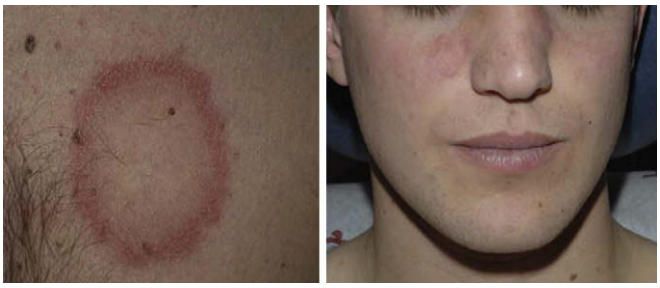

FIG 3. Arcuate and annular plaques with central clearing on the chest of patient 5; malar erythema and focal plaque on the right cheek.

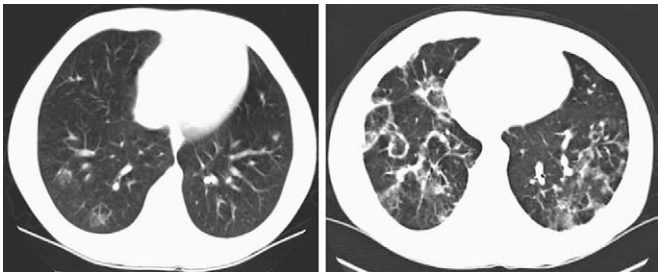

FIG 4. Chest CTs illustrating the fluctuating, circumscribed, rim-enhancing pulmonary infiltrates seen in patient 6 and others.

and multiple oral ulcers. He had no evidence of active infection, malnutrition, or associated gastrointestinal complaints that can sometimes be associated with aphthous ulcers or cheilitis. Over the past 2 years, he had also developed a fluctuating, rim-enhancing, multifocal fluffy pulmonary infiltrate on chest CTs (Fi 4) without associated fevers, respiratory symptoms, or other constitutional complaints. Empiric antibacterial (levofloxacin) and antifungal therapy (itraconazole, voriconazole) had no effect on the infiltrates on repeat CT. Laboratory investigations revealed absence of leukocytosis, ESR 22 to 43 mm/h, and angiotensin-converting enzyme levels 45 to 49 IU/L (normal range, 16-52 IU/L). His ANA was strongly positive at 5.5 EU (0.0-0.9 EU), as was anticyclic citrullinated peptide 33 U (0-20 U). Other normal laboratory tests included CRP 0.49 mg/dL, proteinase-3, anti-dsDNA, ENA, p-ANCA, and c-ANCA. We have followed 3 other patients with CGD with similar appearance of wax-and-wane geographic pulmonary lesions on CT (Fig 4). Biopsies from these other 3 patients with CGD have revealed only interstitial granulomatous inflammation and lymphocytic infiltrates, and all without any evidence of infection. In our experience, treatment with empiric methotrexate in these 3 patients resulted in improvement of pulmonary disease. Because patient 6 remains asymptomatic, no lung biopsies have been performed on him, nor has any specific immunosuppressive therapy been instituted. The oral ulcers are controlled on oral dexamethasone rinse twice daily.

DIFFERENTIAL DIAGNOSIS

In patients 1, 3, 4, and 5, presenting signs and symptoms suggested specific autoimmune conditions (aPL, IgA nephropathy, JIA, and LE). However, in patients 2 and 6 (pericardial effusions and fluctuating pulmonary infiltrates with oral aphthous ulcers), a clear autoimmune diagnosis could not be identified, despite the presence of some features suggestive of autoimmunity.

Venous thromboembolism in childhood is rare and can occur in the presence of endothelial damage, blood stasis, or a hypercoagulable state.[8] Although the first episode of thrombosis in patient 1 occurred in the setting of a venous catheter, the subsequent episodes were not related to any identified triggering events. Lupus anticoagulant, a known risk factor for thrombosis, was present on repeated evaluations of this patient. Although lupus anticoagulant has been reported in patients with CGD as well as carriers,[9] recurrent thrombosis has not been previously described in patients with CGD. The 2006 revised aPL classification criteria require the fulfillment of at least 1 clinical feature (vascular thrombosis or pregnancy morbidity) and 1 laboratory parameter (positive anticardiolipin antibodies and lupus anticoagulant) on equal or more than 2 occasions at least 12 weeks apart.[7]

Pericardial effusion is also uncommon in the pediatric population. Known causes include previous cardiac surgery, infections, connective tissue disorders, and malignancies.[10] The rapid response to prednisone by patient 2 is consistent with pericardial effusions of "sterile" inflammatory origin in childhood, in contrast to a more prolonged course in bacterial pericarditis.[10] Rare cases of cardiac and pericardial involvement in CGD with granulomatous infiltration of the epicardium and myocardium and development of pericardial effusion have previously been reported.[5,11,12]

IgA nephropathy is an immune complex–mediated glomerulonephritis defined histopathologically by mesangial IgA deposit.[13] To our knowledge, there is 1 previously reported case of IgA nephropathy in a patient with CGD, who concurrently had multiple soft tissue abscesses with *Staphylococcus aureus*, thus postulating the role of infections triggering the IgA immune complex formation.[14] Sato et al[15] demonstrated abnormal phagocytic activity in polymorphonuclear leukocytes in 72% of patients with IgA nephropathy, implicating the role of neutrophils in the clearance of IgA-containing immune complexes and therefore preventing their accumulation in the glomeruli.

The differential diagnosis of new onset polyarthritis includes postinfectious (Reiter syndrome) rheumatic fever, in association with inflammatory bowel disease, and psoriatic arthritis. However, the association of symmetrical polyarthritis with multiple large and small joints, the presence of rheumatoid nodules, and RF seropositivity is consistent with JIA.[16] JIA was previously reported in 1 patient with CGD, whose clinical course was similar to that of patient 4 reported here.[4] Cutaneous LE is well described in CGD carriers and more recently in patients with CGD.[9,17,18] Of note, the diagnosis of cutaneous lupus in his mother suggests a shared genetic susceptibility.

The differential diagnosis of pulmonary infiltrates in the context of CGD includes bacterial, fungal, or viral pathogens. However, the characteristic CT pulmonary appearance or pattern of patient 6, which did not respond to or have any correlations with empiric antibiotic and antifungal treatment or leukocytosis, suggested a noninfective etiology. Of note, similar rim-enhancing lesions with a characteristic wax-and-wane pattern over a period of years have been observed in 3 other patients with CGD. Over time, these patients reported dyspnea on exertion and demonstrated oxygen desaturation after exercise. They were without leukocytosis, fevers, or chills, and lung biopsies failed to demonstrate any infectious pathogens. Treatment with empiric methotrexate in these 3 patients resulted in improvement of pulmonary

disease. This constellation of photosensitive rash, oral aphthous ulcers sensitive to oral dexamethasone elixir, and distinct geographic pulmonary lesions in patient 6, in the absence of autoantibodies or other organ involvement, do not fit within the criteria for any known autoimmune diseases.

LABORATORY AND OTHER TESTING/ PROCEDURES

The diagnosis of CGD in each case was confirmed by dihydrorhodamine 123 assay, Western blot, and in all but patient 4 (p47 deficiency), genomic sequencing mutation analysis. Laboratory and other testing specific for each case is described.

DISCUSSION OF PATHOGENESIS

There is an increasing awareness of autoimmune phenomena in PIDs, particularly PID associated with lymphoid and humoral defects.[19] The most frequently described immune-related inflammatory disorders in CGD are inflammatory bowel disease and LE. CGD-associated colitis is clinically and histologically similar to Crohn disease but appears distinct from the typical granulomatous lesions causing obstruction in the gastrointestinal and urogenital system.[6] Discoid lupus is most commonly reported in female carriers of X-linked CGD, although it has been described in patients with CGD as well.[9,20] Isolated case reports of other immune-mediated phenomena in patients with CGD include SLE,[4,21] autoimmune thrombocytopenia,[22] idiopathic thrombocytopenic purpura,[23] rheumatoid arthritis,[3] eosinophilic cystitis,[24] IgA nephropathy,[14] sarcoidosis,[2] and celiac disease coexisting with pulmonary hemosiderosis.[25]

Classically, the definition of an autoimmune disease requires the detection of an autoimmune response (autoantibody or cell-mediated), the identification of a corresponding autoantigen, and induction of such response and disease in experimental animals.[26] However, more recently, there has been a broadening list of parameters for diagnosis of an autoimmune disorder,[27] in particular, the inclusion of clinical response to immunosuppression as a diagnostic criterion. The most consistent feature of the cases presented here, with the exception of case 6, is the remarkable response to immunosuppressive therapy. Also striking is the relative rarity of these conditions in the general population, particularly in childhood. In patients with CGD followed by our clinic, 13 have an AI disorder, making up more than 10% of our cohort. This does not include patients who have inflammatory bowel disease, which is not uncommon in patients with CGD, occurring in some 30% of the patients followed at NIH.[6] Given that our program receives referrals of patients with more complex problems associated with their CGD, it is possible that our patient population may not be representative of the general clinical immunology community. It would be of great value to ascertain the prevalence of autoimmune manifestations in CGD from all available registry databases that track patients with CGD.

We believe that these autoimmune disorders are not simply part of the inflammatory spectrum seen in CGD, because these unusual presentations are outside the range of what is commonly seen in this disease. Nor are they isolated phenomena coincidentally observed in patients with CGD. Rather, the new hypothesis that we propose is that patients with CGD are at increased risk of developing any of a large spectrum of known and unknown types of specific autoimmune diseases. The type of autoimmune disease that develops likely has a specific genetic basis or susceptibility risk and/or environmental triggers. Iatrogenic factors that could affect development or exacerbation of autoimmunity include trimethoprim-sulfamethoxazole, itraconazole, or IFN-γ. In this context, we propose that patients with CGD who satisfy established diagnostic criteria for a specific autoimmune disease such as IgA nephropathy, sarcoidosis, LE, or JIA actually have these disorders and are not just a mirror phenotype that represents part of the spectrum of CGD inflammation. Furthermore, this paradigm provides a basis for viewing the recurrent thrombosis or aPL (patient 1), the recurrent pericardial effusion syndrome (patient 2), or the recurrent aphthous ulcers with fluctuating pulmonary infiltrates (patient 6) as autoimmune diseases that respond to immunosuppressive therapy.

FINAL DIAGNOSIS AND TREATMENT-MANAGEMENT PLAN

Chronic granulomatous disease acquired its original nomenclature from the signature pathognomonic clinical feature of this disorder, the widespread multiorgan occurrence of characteristic multinucleated giant cell granulomas. When these are manifested in and around hollow organs such as in the gastrointestinal or genitourinary systems, they cause pyloric/small bowel obstruction and ureter/bladder outlet obstruction, which are rapidly steroid-responsive. Another generalized manifestation of this exuberant granuloma forming process includes impairment of wound healing that paradoxically is improved with steroids. Furthermore, studies in CGD knockout mice of both the $gp91^{phox}$-deficient X-linked and the $p47^{phox}$-deficient autosomal recessive varieties have demonstrated that inhalation of sterilized nonviable *Aspergillus* spores can cause acute pulmonary decompensation from rapid granuloma formation that is not seen in normal mice,[28,29] and injection of a sterile stimulus of inflammation into the peritoneum of CGD mice elicits a robust cellular inflammation response that is an order of magnitude greater than seen with normal mice.[1] Recent studies have demonstrated that neutrophils of patients with CGD have delayed apoptosis associated with diminished production of anti-inflammatory mediators relative to normal neutrophils, providing another mechanism by which inflammation in CGD is prolonged with impaired resolution.[30] Heretofore, the prevailing paradigm has been that all manifestations of inflammation in CGD are just extremes in the spectrum of CGD granuloma formation, including uncommon presentations as well as presentations that fulfill specific diagnostic criteria for well characterized autoimmune disorders. Some types of inflammation, such as those characteristic of Crohn-like inflammatory bowel disease in its most mild and low-dose steroid–responsive form, occur with such high frequency in patients with CGD (more than 20% to 30% of patients) that under the prevailing paradigm, this inflammatory bowel disease has been viewed as part of the CGD granuloma spectrum. However, a subset of patients with CGD with inflammatory bowel disease has severe Crohn-like colonic disease associated with extensive bloody diarrhea, strictures, and fistula formation. It is not clear whether these patients actually have Crohn disease triggered by CGD, or have a CGD-specific process.

Recently, it has been shown that T lymphocytes exhibit a very small burst production of reactive oxygen products in response to mitogen stimulus, and that a portion of this burst is missing in

mouse and human CGD T lymphocytes.[31] In the murine CGD model, $CD4^+$ T lymphocytes had a strong bias toward a T_H1 pattern of cytokine production when differentiated to an effector phenotype,[31] and when challenged with pulmonary aspergillosis, led to excessive inflammation and a dominant production of IL-17.[32] This further raises the possibility that CGD is a risk factor in the development of T_H1 types of autoimmune diseases. Although some long-term medications that patients with CGD receive, in particular IFN-γ, may influence this risk, data from CGD mouse models not on medications have undeniably demonstrated that CGD is associated with excessive inflammation. Our current study lacks the statistical power to address the potential contribution of any particular medication on the development of autoimmunity in CGD. We hypothesize that all patients with CGD are at significantly increased risk of developing autoimmune disease, but that the actual expression of a particular autoimmune disease is likely a result of a combination of familial genotype and environmental exposure factors.

The new paradigm we propose is that manifestations of autoimmune diseases in CGD that meet established diagnostic criteria for a particular autoimmune disease be regarded as such and not as only part of a broad spectrum of granuloma formation associated with CGD. This has important therapeutic implications in that, in addition to corticosteroid therapy, appropriate steroid-sparing therapies for that autoimmune disease should be initiated to treat the disease pathology. Without this paradigm shift, there seem to be significant barriers to consideration of the use of potent steroids and steroid-sparing immunosuppressant therapy such as anti–TNF-α agents, methotrexate, azathioprine, or even cyclosporine A or tacrolimus in CGD because of the fear that the increased risk of infection in a patient with CGD would outweigh the potential benefits. Although there probably is an increased infection risk associated with use of potent nonsteroidal anti-inflammation agents in patients with CGD, those patients with CGD with autoimmune disease who do not respond to prednisone or who require more than low-dose alternate-day prednisone for symptom control should be considered for treatment with nonsteroidal agents with established and known efficacy in treatment of the specific autoimmune disorder, albeit with close clinical monitoring.

SUMMARY

Although infections and granuloma formation are undoubtedly the most common manifestations in patients with CGD, there is a significant subset of patients with CGD who experience a broad variety of autoimmune diseases, which respond well to immunosuppressive therapy. To explain the diversity of autoimmune disorders observed in patients with CGD, we suspect that CGD might itself serve as a genetic cofactor, which lowers the threshold for overt phenotypic development of autoimmunity, and in which the particular type of autoimmune disease manifested is dictated by the genetic and/or environmental background. This is a new paradigm that will require additional observational input with statistical assessment, but it has specific implications for clinical management. Maintaining a high index of suspicion for autoimmune disorders in patients with CGD will minimize unnecessary invasive procedures and allow early institution of appropriate therapy to control inflammation and reduce risks of long-term complications. Furthermore, reporting of additional cases will allow identification of common patterns of disease and will help direct appropriate studies and eventually lead to a better understanding of the pathogenesis of autoimmune disorders in patients with CGD.

Key messages

- **Autoimmune diseases should be considered early in the differential diagnosis of patients with CGD, particularly in the absence of identifiable microbial pathogens.**
- **Supportive laboratory parameters should be actively sought for, for example, serologic markers of autoantibodies, RF, and serum angiotensin-converting enzyme.**
- **Despite the immune-compromised state of patients with CGD, although it may appear paradoxical, prednisone and/or other immunosuppressive drugs are often beneficial or necessary in these autoimmune conditions, and appropriate therapy should be not be withheld because of concern over risk of infection.**

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