Photocopy Machines and Occupational Antiphospholipid Syndrome

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Abstract

Two patients who worked for several years in the operation and maintenance of photocopy machines developed an autoimmune disease. In both, early manifestations were thromboembolic phenomena associated with anticardiolipin antibodies. Joint and kidney involvement emerged later, with the appearance of other autoantibodies. These two patients were occupationally exposed to ultraviolet irradiation, ozone emission, and possibly some oxides of heavy metals. To our knowledge this is the first report of occupational autoimmune disease in photocopy machine workers, and the first description of antiphospholipid syndrome as an occupational disease. The possible cause-effect inter-relationship between their occupational exposure and autoimmune disease is discussed.

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Autoimmune disorders are complex entities involving a genetic predisposition with environmental trigger factors playing an important role in their development, and although an association between occupational exposure and autoimmune disorders has been proven for some disorders, the antiphospholipid syndrome has not, to our knowledge, been associated with any specific occupational exposures. We present two patients with an autoimmune disorder who developed their disease after prolonged work with photocopying machines. In both, thromboembolic phenomena were noted and anticardiolipin antibody was found, confirming the diagnosis of APS. Clinical and laboratory features alluding to the diagnosis of systemic lupus erythematosus emerged later.

Patient Descriptions

Patient 1

A 35 year old man, a copying machine technician, was evaluated for a possible association between his clinical condition and his occupational exposure. He was completely healthy until the age of 30, when he noticed swelling, tenderness and redness of his left ankle. Evaluation at the time suggested superficial phlebitis, and aspirin was recommended. His condition did not improve, the leg edema continued, walking was painful and he developed stasis dermatitis. One year later plethysmography and duplex analysis demonstrated venous insufficiency and a non-occlusive thrombus in the left popliteal vein. The thrombo-occlusive events recurred, involving other veins in both the lower and upper limbs.

Laboratory tests revealed mild thrombocytopenia 69,000–132,000/mm^3 (normal > 150,000/mm^3), immunoglobulin G anticardiolipin of 125 IU, IgM anticardiolipin 84 IU, and anti-beta-2 glycoprotein-I of 84 IU. Protein S and C and antithrombin III were all within normal limits. Antinuclear antibodies were not detected.

Several months later he complained of fever, cough, dyspnea and pleuritic pain. Chest X-ray showed a pulmonary infiltrate in the right upper lobe. He improved on azythromycin, but since the symptoms recurred and hemoptysis was noted, he was admitted to hospital. Physical examination revealed decreased breath sounds in the lower half of the right lung, without rales, and sensitivity with chronic skin changes in the left leg. Platelet count was 76,000 mm^3, lactate dehydrogenase IU/L, aspartate aminotransferase 54 IU/L, and creatine phosphokinase 478 IU/L. Chest X-ray revealed a large infiltrate on the right lower lobe and several infiltrates in the left lung. Blood and sputum cultures were negative, as was serology for Mycoplasma and Legionella. Although suggestive of pulmonary embolism this diagnosis was not pursued and he was discharged on aspirin therapy. Only upon worsening of his leg condition was anticoagulation with warfarin instituted.

Four years later he noted joint and abdominal pain and fatigue. Antinuclear antibody titer was 1:640 with a homogenous pattern, anti-DNA was 98 IU/ml and rheumatoid factor 64 U/ml. Anticardiolipin antibody titer rose to 184 IU, and complement C3 level was 45. Proteinuria was 430 mg/24 hours (normal < 240) and microalbumin 301 mg/24 hours (normal < 30). Treatment with hydroxychloroquine sulphate (Plaquenil®) 400 mg daily was added.

The patient had worked as a technician repairing and maintaining photocopying machines from the age of 24. This involved replacing faulty parts, loading the machines with the required chemicals and replacing the toner cartridges. He repaired both dry and "wet" type photocopying equipment. Every day he had to activate photocopying machines several hundred times, often with the protective glass plate removed. Because of the severity

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APS = antiphospholipid syndrome
Ig = immunoglobulin

of his symptoms he was unable to continue working and he quit his job. He had done this work for 11 years.

Two years later, despite not having occupational exposure, his anti-DNA is still 404 IU/ml, ANA titer rose to > 1:2560, IgG and IgM anticardiolipin titers are 123 IU/ml and 68 IU/ml respectively. He suffers mainly from the consequences of the occlusive events

Patient 2

A 30 year old man who worked as a printer and photocopy shop manager was evaluated for a possible association between his complaints and his occupation. He had been healthy until the age of 21 when he was admitted for pain and swelling of his left calf, which was diagnosed as deep vein thrombophlebitis. He was treated with heparin and discharged with a prescription for enoxaparine and acenocoumarol for 3 months, during which his leg did not improve and ulcers developed.

Six months after stopping anticoagulation as recommended, he experienced another episode of DVT, this time in the right calf. Anticoagulation was resumed for 6 months. Several days following cessation of anticoagulation, he experienced excruciating chest pain and was admitted due to acute myocardial infarction with a complete obstruction of the left anterior descending artery, which responded completely to thrombolytic therapy. IgG and IgM anticardiolipin antibody levels were 67 and 87 IU/ml respectively, and chronic anticoagulation with warfarin was instituted. Two years later he reported joint pain involving his hands. ANA titer was 1:1280, anti-DNA 54 IU/ml, and anti-double-stranded DNA antibodies were found. Treatment with Plaquenil 400 mg/day was begun. Two vascular bypass operations in the legs failed and he continued to suffer from chronic leg ulcers and recurrent infections, which impaired his ability to walk and his capacity to work as well as his daily routine. Recently he underwent amputation of his left foot due to pain and the development of gangrene

This patient's occupation, running a photocopy center, involved the daily operation and maintenance of about 20 photocopy machines as well as several other stencil and printing machines. He also activated these devices hundreds or even thousands of times daily, and replaced toners and fluids required for the copying processes. Most of the daily maintenance of the machines was done by him to reduce expenses.

Discussion

These two male patients developed a severe thromboembolic disease, both venous and arterial, at a young age, leaving them handicapped and unable to work. Neither patient had a family history of autoimmune disorders, and both exhibited findings primarily of antiphospholipid syndrome and later some clinical and laboratory signs of SLE. They worked in a similar occupational environment, operating photocopy machines, of diverse manufacturers, hundreds of times every working day and loading toner cartridges daily. It is tempting therefore to associate their illness with this exposure.

Most photocopy machines use the xerographic method that makes copies on plain paper. A charged photoconductive drum receives light reflected from the original, creating a charged latent image that attracts toner particles. These are transferred onto paper and fused by heat or pressure. The toner consists of black carbon particles in a resin binder. The light source used in these machines is either continuous, which is common to most office machines, or a flash lamp that is used in the larger and faster machines; the lamp is fluorescent, metal halide or quartz. The light source emits mainly visible light but some machines do emit substantial ultraviolet below 300 nanoM. Ozone is generated from the reaction of charged ions and electrons with atmospheric gases Since most photocopy machine drums are made of selenium, small amounts of selenium, arsenic or cadmium oxide can also be found in the room.

Ultraviolet B has been shown to increase apoptosis of kertinocytes where low doses facilitate capsase-dependent apoptosis in which Sm and Ku autoantigens and DNA are translocated to the surface of the early apoptotic cell. Higher doses lead to perturbed apoptosis with altered morphology, slower DNA fragmentation. and Sm, Ku and DNA concentrating on the cell membrane Toxic irradiation causes cell necrosis with autoantigens diffusing into the surrounding milieu, exposing internal cellular and nuclear contents to the immune system and to the possible induction of autoantibodies. In our patients, the ultraviolet exposure caused increased apoptosis that was beyond the capacity of the macrophage system to handle the load, resulting in the immune system encountering intracellular antigens and developing autoantibody [1].

These patients absorbed small doses of UV with each operation of a photocopy machine, as the exposure as each activation lasts several seconds only and the UV emitted is of low energy. However, due to many exposures during a day's work the total daily occupational exposure of the two patients to UV was considerable, and although non-erythmogenic, long exposure to UV of lesser photon energy such as emitted from fluorescent sources has been shown to have a similar effect on dendritic cells as short exposures to stronger energy UVB [2].

UV and high concentrations of ozone in ambient air induce reactive oxygen species in exposed tissues, increasing production of the highly reactive hydroxy radical (*OH) and increasing chronic oxidative stress in exposed animals and humans. An increase in chronic oxidative stress, which may lie at the heart of autoimmunity as it leads to oxidation and nitration of proteins rendering them to the immune system as neo-antigens, has been demonstrated in photocopy machine workers exposed to these emissions, as evidenced by an increase in lipoperoxidase level in plasma and red blood cells as well as reduced levels of super-oxide dismutase, catalase and glutathione peroxidase, and correlated to work load as expressed by the number of machine activations [3]. An increase in DNA damage and a decrease in

ANA = antinuclear antibody
DVT = deep vein thrombophlebitis
SLE = systemic lupus erythematosus

UV = ultraviolet

nucleic acid repair have also been described in photocopy machine workers [4]. Thus, operating a photocopy machine increases oxidative stress, via ozone emission and UV irradiation, and leads to an increase in apoptosis and cellular damage, resulting in the development of autoimmunity.

The primary clinical presentation in our patients was APS, and only later did they manifest symptoms, signs and laboratory findings suggesting SLE. This observation corresponds with the findings of cardiolipins moving from mitochondria to other cellular membranes and appearing early on the cellular membrane during cell death and even during activation-induced apoptosis, reaching the outer surface of the cellular membrane and displaying these internal antigens to the immune system [5].

Although direct evidence for *de novo* induction of autoimmune disease in humans by UV, ozone or any other exposure is lacking, one could postulate the unusual exposure of the above described patients as a cause, also taking into account a genetic predisposition to autoimmunity. UV irradiation causing increased apoptosis and exceeding macrophage capability to phagocytose on the one hand, and chronic oxidative stress induced by ambient ozone, metal oxides or other emissions on the other, lead to increased introduction of cardiolipin on the cell membrane, the production of anticardiolipin antibody and the development of APS. Continued exposure to the copy machine, together with the presence of serum anticardiolipin antibody increased chronic oxidative stress, leading to further disruption of cells and exposing more cell inner contents to the immune system, which culminated in the diagnosis of SLE. We therefore raise the possibility that excessive work with photocopy machines may lead to the development of autoimmune disorders, and that antiphospholipid syndrome in the above described patients was an occupational disease.

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