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AN UNUSUAL AUTO-IMMUNE SYNDROME[1]

A Follow-up with Reference to Breast Hypertrophy, Systemic Lupus Erythematosus and Verrucae

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Abstract. A twelve-year follow-up on a young woman previously reported to have mammoth benign breast hypertrophy, extensive erythema annulare centrifugum and generalized melanoderma supports the view that her syndrome was another variant of systemic lupus erythematosus. Virtually complete removal of the breasts was essentially curative. In contrast is the fact that the patient's sister died of nephritis due to proven systemic lupus erythematosus.

The subsequent development of herpes zoster at the early age of 28 and the growth of hundreds of exuberant viral warts which have persisted for 7 years despite multiple therapies suggests out patient has a diminished cellular immunity to virus infection. Correlation is made with the published reports of virus-like particles in lupus tissue and the evidence of a viral factor in the "lupus syndrome" which occurs in inbred New Zealand mice. Accordingly, altered immune responses to chronic viral infection may explain the benign breast hypertrophy as well as the systemic and familial lupus our patient presented.

Twelve years ago we reported a young woman with a unique triad of findings: enormous bilateral breast hypertrophy, generalized melanoderma and finally thousands of pruritic poly-cyclic bands undergoing continuous migration over her skin surface (17). The patient proved to have specific circulating antibodies to her own cystic breast tissue, and her serum repeatedly showed a strongly positive L.E. phenomenon.

The syndrome of progressive bilateral benign breast enlargement, generalized pruritic arcuate migratory ridges and generalized severe darkening of the skin had been present for over 5 years. Following mammoplasty in which 13.5 pounds of breast tissue was excised, there was a dramatic resolution of the erythema annulare and involution of the melanoderma, and reversal of the positive L.E. test. The residual lesions were suppressed by an oral dose of 4 mg of triamcinolone daily.

All this defied simple clinical classification and was hence labelled as an unusual auto-immune syndrome consisting of mammopathy, melanoderma and erythema annulare centrifugum. Nonetheless one could cogently argue that the entire syndrome was a rare form of systemic lupus erythematosus. In favor of this we cited the following: (*a*) repeatedly strongly positive L.E. tests, (*b*) leukopenia, (*c*) biologic false positive STS, (*d*) clinical malaise, (*e*) elevated sedimentation rate, (*f*) elevated γ globulin, (*g*) response to steroid, (*h*) erythema annulare centrifugum may be cutaneous sign of S.L.E., (*i*) pigmentation is a hallmark of certain forms of lupus erythematosus.

Thus, only the enormous virginal breast hypertrophy remained outside the pale of previous clinical experience.

We wish now to report briefly on this patient's subsequent 12 years course. All that has transpired supports the view that (1) her disease is systemic lupus erythematosus, (2) she lacks cellular antiviral immunity, and (3) surgical excision of the breasts was an effective therapeutic measure.

CASE REPORT FOLLOW-UP

The patient, now 38 years of age, has remained under our regular care and observation during the 12 year interval since the original publication. The removal of virtually both breasts was followed by a dramatic sub-

[1] Presented as part of the Sven Hellerström Lecture in Stockholm, September 24, 1971.

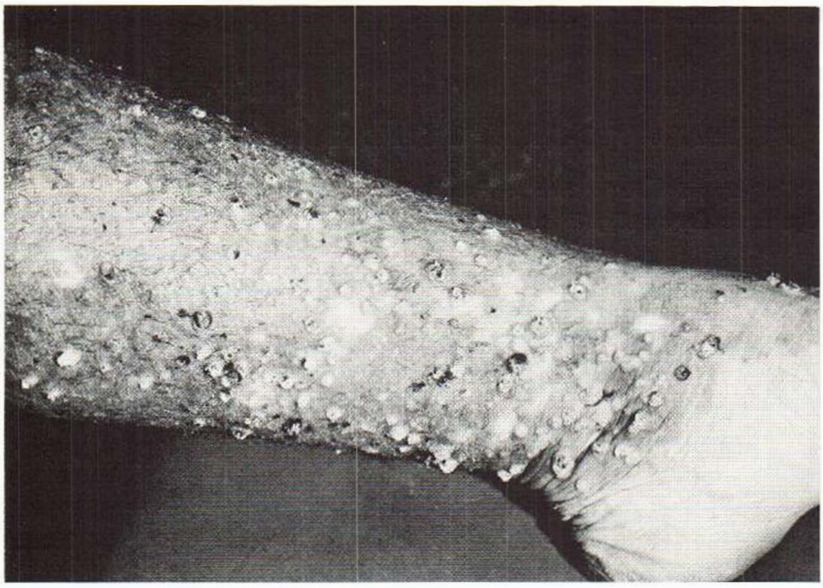

Fig. 1. Extensive florid growth of warts of the leg of patient with systemic lupus erythematosus. The dorsa of the hands were similarly involved.

sidence in the cutaneous and serologic changes. The pruritic gyrate bands became few in number, but for complete control required a maintenance dose of oral triamcinolone 4 mg every other day. This requirement has persisted to the present. The pigmentation gradually lessened over a period of years and now the skin is normal in color. At this time the patient has no skin changes but she states that stopping the steroid for a week or more will be followed by a recrudescence of a few urticarial bands. The blood studies (Table III) show a continued elevation of the gamma globulin level, but the L.E. test has remained negative to weakly positive.

In the early years the patient experienced a premenstrual exacerbation, but oral challenge with progesterone was without effect. At no time have the breasts shown enlargement of the residual tissue.

There have been three pregnancies, 1, 2 and 4 years after the breast surgery. The first, a neonatal death at 6 hours, the second resulting in a healthy normal child, and the third in a miscarriage at 4 months. At the age of 28, two years after the surgery, our patient developed a severe herpes zoster which responded to treatment and left no scars.

Six years post-operatively, we first noted six rather large warts on the shins. Within 2 years they had increased in number to over thirty and by 1968 they completely covered both lower legs (Fig. 1), and were present on the dorsae of the hands. Biopsy disclosed the diagnostic patterning of verruca vulgaris (Fig. 3). Despite persistent regular treatment the warts have remained the primary problem and are completely refractory (Table I) (Fig. 2).

Our patient's health remains good. At the present time her biochemical parameters contrast favorably with those previously recorded (Table II).

From the family history standpoint, within a year after our publication (17) the patient's younger sister was found to have a biologic false positive serologic test. This was identified years later as a sign of systemic lupus erythematosus, long after she had experienced five miscarriages. Lupus nephritis, severe hemolytic anemia, and thrombocytopenia became her major problems requiring repeated hospitalizations. Despite a wide variety of therapy and a nephrectomy as a result of a renal infarct in 1970, her sister died of her nephritis this year. One brother and her mother are in good health. The father is not living.

Table I. *Treatments used unsuccessfully over seven-year period in attempt to eradicate exuberant growth of warts in patient with history of systemic lupus erythmatosus* (*Fig. 1*)

Anthralin	Iodine
Bistrimate	Iodo-deoxy-uridine
Cantharidin	Liquid nitrogen
Castellani paint	Phenol-nitric acid
Curettage-electrodesiccation	Podophyllin
5-Fluorouracil	Poison ivy antigen
Formaldehyde	Retinoic acid
Gamma globulin-sublesional intramuscular	Salicylic acid plaster
Glutaraldehyde	Sulfur
Grenz ray	Vitamin A (500 000 U/day)

DISCUSSION

The surprising appearance of great numbers of large verrucae on the legs and hands of our patient previously reported to have enormous breast hypertrophy and the findings of systemic lupus erythematosus calls for a review of her viral status. The remarkable resistance of the warts to

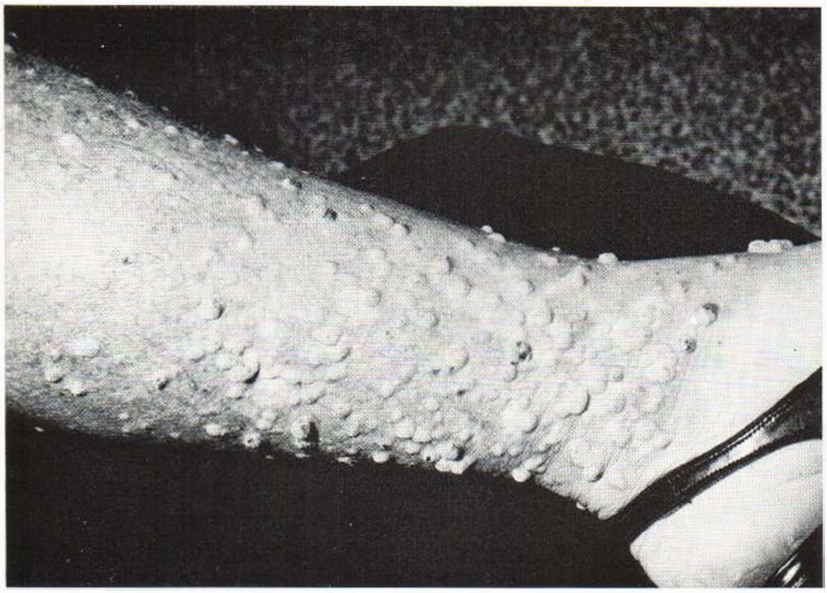

Fig. 2. One year later. Warts have become more exuberant despite intensive treatment (Table I), suggesting an absence of viral immunity.

intensive diverse long-term therapy (Table I) suggests a failure of the patient's intrinsic antiviral cellular immunity. This could involve a defect in interferon production or in the thymus dependent lymphocytes. We doubt that it is related to the years of minor steroid dosage which averaged 2 mg oral triamcinolone daily.

The episode of herpes zoster at the early age of 28 is another sign which may be interpreted as reflecting a diminished capacity to combat viral infection.

All this is significant in light of the current growing interest in the possible role of viruses in the pathogenesis of systemic lupus erythematosus. Virus infection has been implicated in several tangential ways. The study of a spontaneously appearing lupus syndrome in hybrid New Zealand mice—NZB/NZW F, Hybrid (B/W)—has been most rewarding (18).

These mice develop anemia, splenomegaly and glomerulonephritis. As many as 75 % show a positive L.E. test, and the nephritis is of an immune complex type as seen in man. Again, remarkably, the disease is milder in the male mice. Careful study reveals the circulating antibody response to be excessive whereas the thymus-derived cellular immune response is depressed. As a result, viral infections flourish in these animals and a slow type virus late in appearance presumably accounts for the clinical expression. The mouse incapable of suppressing or eliminating the viral infection by cellular immunity continues to elaborate an enormous amount of circulating antibody from a hypertrophied antibody cell system. This in turn

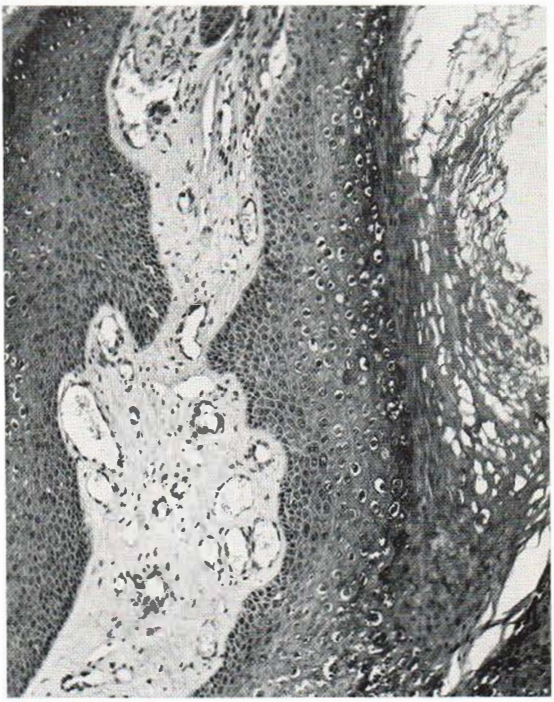

Fig. 3. Histologic patterning of wart showed no unusual findings. × 77.

Table II. *Sequential comparison of key laboratory studies on systemic lupus erythematosus patient before and after breast excision*

	Nov. 1958 3 months Preop.	June 1959 6 months Postop.	Sept. 1971[a] 12 years postop.
White cell count:			
Total	4 000	4 500	5 000
Neutrophils	41 %	49 %	80 %
Eosinophils	32 %	3 %	1 %
Lymphocytes	25 %	3 %	15 %
Monocytes	2 %	45 %	4 %
L.E. test	strongly positive	negative	negative to weakly positive
S.T.S.			
Kolmer	3+ reactive		
Kline	3+ reactive	2+ reactive	1+ reactive
Sedimentation rate	45	28	—
Plasma proteins			
Albumin	3.1	3.9	4.4
Globulin	4.2	3.1	4.3
$a1$	0.33	0.27	0.22
$a2$	0.69	0.64	0.76
B	0.79	0.92	0.99
γ	2.41	1.23	2.38
Circulating autoantibody to cystic breast tissue	+ (dil. 1:8)	+ (dil. 1:8)	—

[a] Additionally, cholesterol, calcium, phosphorus, creatinine, uric acid, SGOT, SGPT, alkaline phosphatase, CBC, platelet count and urinalysis were normal.

produces the deleterious inflammatory effects in the kidney and elsewhere at the site of antigen-antibody immune complex deposition. Such a mouse model of lupus has proved most instructive.

Support for such a genetic thymic defect in cellular antiviral immunity and a compensatory hyperimmune response to the chronic viral antigenemia is seen in human patients with lupus (10). Studies by Hollinger et al. showed specific circulating antibodies to 15 different viral antigens were higher in 31 lupus erythematosus patients than in their matched controls. Such a hyperimmune antibody state is also reflected by the hypergamma globulinemia generally present (4).

The postulated failure of lupus patients to eradicate viral infection is also supported by the recent observation of Alarcon-Segovia & Fishbein (1) that 25% carry the Australian antigen, a presumed portion of the virus of serum hepatitis. In normal healthy individuals this antigen is not commonly present in the blood.

More direct evidence of the association of virus infection and the lupus patients has been the discovery of virus-like particles in the endothelium of the renal glomeruli of patients with systemic lupus erythematosus. Gyorkey & Sinkovics (6) were the first to find and propose that these endoplasmic reticulum-bound microtubular structures represented a myxovirus. The observation has been repeatedly confirmed (12, 2, 14, 8) but its viral nature doubted since the tubular structures are interpreted by others as a simple membrane-bound inclusion, due to non-specific injury (7). Noteworthy is the fact that the virus-like inclusions measure 230° A in diameter, and are digested by RNase but not DNase. They are found in the circulating leukocytes of systemic lupus as well as in the endothelium of lesions of discoid lupus erythematosus, scleroderma, dermatomyositis and congenital rubella (9). They have also been observed in the vascular endothelium of muscle in L.E. and polymyositis as well as in the synovial tissue from rheumatoid arthritis (8), and in tissue culture of lymphoid cells (16). Despite the failure of careful studies to isolate any virus from these tissues (5), or to show any specific antibodies (16), the idea that the inclusions are viral is still viable since isolation may require sophisticated measures such as cell fusion and or helper viruses. Furthermore, the absence of a viral protein envelope could explain the absence of diagnostic antibodies (7).

Although it was not possible to do serologic studies on our patient's family, the concurrent onset of systemic lupus erythematosus in our patient's sister, and its typical lethal involvement of her kidneys (15) underscores the genetic factor as expressed in the familial incidence. In a pair of monozygotic twins, Jokinen & Jankala (11) have shown a dramatic virtual identiy of their titre patterns of circulating antibody to cell nuclei, DNA, heart extract, thyroid microsomes, thyroglobulin and erythrocytes.

To search for the unifying theme, we would propose that our patient, genetically deficient in thymus-derived lymphocytes, developed breast hypertrophy as a result of a mammotropic proliferative virus, manifesting itself at puberty. The chronic release of viral or nuclear antigen over the years induced an enormous compensatory output of circulating antibody (Table III). In turn the resultant circulating antigen-antibody complex

was in such amount as to precipitate in the breast, the skin and elsewhere. In the breast it produced widespread hematoxylin bodies identified later on review of the histologic sections. It was this same complex that produced the L.E. cell phenomenon, which in turn disappeared once the breasts were essentially removed. We presume again that the complex deposited in the skin, but strangely not in the kidney (13), accounted for the generalized waves of urticaria, and the chronic post-inflammatory melanoderma. Once the postulated source of the viral antigen, namely the breast, was virutally removed, the skin changes became minimal. In this line of reasoning, were the sister's primary viral infection to have been in the kidneys, the course was inexorable since ablation of this vital organ was not possible.

Although the breast was not previously known to be involved in lupus (4), no system can be considered exempt. Thus the recent report of Diederichsen & Pyndt (3) has disclosed for the first time antibodies to neuronal cytoplasm.

The early onset of herpes zoster and the enormous proliferation of warts are likewise signs of a lowered viral immunity. In our patient inapparent chance exposure to the wart virus led to easy implantation and ready inoculation on sites of epidermal abrasion from shaving. It is likely that specific cell resistance to viral infection is impaired here. Indeed, experimental studies on the animal analogue of warts, the Shope papilloma, reveal a central role for cellular immune processes in the appearance and course of this viral tumor (9). The absence of a recurrence of the erythema annulare, pigmentation and serologic signs of L.E. bespeaks a failure of the circulating antibody system to respond in an abnormal quantitative way to the wart tissue. This would be in presumed contrast to the documented response to the breast tissue.

It is apparent that the threat of viral infections is a serious continuing one for our patient.

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