American Journal of Hematology 51:93–97 (1996)

LETTERS AND CORRESPONDENCE

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Refractory Thrombotic Thrombocytopenic Purpura Treated With Cyclosporine

To the Editor: Thrombotic thrombocytopenic purpura (TTP) is an uncommon disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, fluctuating neurologic changes, fever, and renal disease [1]. We report a case of TTP that responded to cyclosporine after failing to respond to multiple different therapies.

A 31-year-old African-American woman presented in the 29th week of pregnancy. Her platelet count was 17,000/μl, hematocrit 21% with red cell fragmentation and decreased platelets on peripheral smear, and urinalysis showed protein. Lactic dehydrogenase (LDH) (459 IU/L) and bilirubin (26 μmol/L) were elevated. Caesarian section revealed an unremarkable placenta. On day 7 the patient remained anemic and thrombocytopenic. Intravenous immunoglobulin (IVIg) was given. On day 10 prednisone 1 mg/kg/day was started. Elevation in serum creatinine led to the suspicion of hemolytic uremic syndrome (HUS)/TTP. On day 15, five cycles of plasmapheresis were started. IVIg was repeated. On day 24, the patient was discharged with a platelet count of 50,000/μl and an LDH of 497 IU/L, on prednisone 80 mg/day.

One month later, her platelet count was 25,000/μl, hematocrit 26%, serum creatinine 265 μmol/L (3.0 mg/dl), and LDH 2,070 IU/L. TTP was diagnosed, and plasma exchange, IVIg, Danazol, and Solumedrol were instituted (Fig. 1). Splenectomy was performed, with pathology showing focal platelet-fibrin thrombi in arterioles and venules, consistent with TTP. Plasma exchange was restarted on day 8, totalling 38 cycles. High-dose Solumedrol was given. Renal failure necessitated hemodialysis. Severe gastrointestinal bleeding occurred on day 17. Pulmonary hemorrhaging on day 21 required intubation. Random donor platelets were transfused because of continued hemorrhaging. Vincristine was tried. The patient developed fevers without infection and fluctuating neurologic signs with negative neurologic workup. Cyclosporine was started on day 42, titrated to maintain monoclonal levels at 200 ng/ml. Improvement in clinical status began within 24 hours. The patient was extubated on day 44. Mental status began clearing on day 47. Plasmapheresis and steroids were discontinued. The platelet count rose to 243,000/mm^3 and LDH decreased to 383 IU/L by discharge (Fig. 1). Ten months later, she is being maintained on cyclosporine and hemodialysis, with a platelet count of 432,000/mm^3 and an LDH of 200 IU/L.

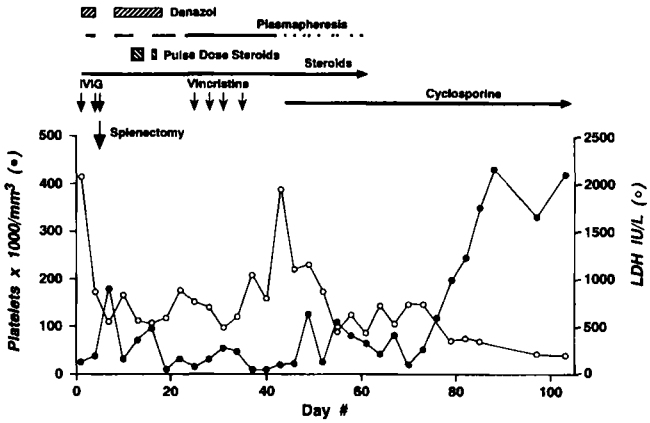

Fig. 1. Course of therapy in patient with TTP.

We have described the second case of TTP in the literature responsive to cyclosporine [2]. This patient's disease was extremely refractory, even after receiving virtually every therapy known to be effective. The number of rounds of plasmapheresis and the volume of plasma infused were greater than that used successfully in prior trails [3]. Infusion of the cryosupernatant fraction of plasma was tried without success.

Cyclosporine is an immunomodulatory agent used to prevent rejection following organ transplantation [4]. It is thought to work by inhibiting T-cell activation, which apparently leads to the inability to transcribe T-cell genes that encode for cytokines such as interleukins 2, 3 and 5 [4]. These cytokines help to initiate and potentiate the immune response. In TTP, an initial inciting event may occur, such as infection or toxin exposure. This could stimulate the cascade of events involved in the TTP syndrome, which may then depend upon interleukins and other cytokines for perpetuation. This disease process possibly involves continued release of antibodies to endothelium, platelet agglutinating factors, or unusually large von Willebrand factor multimers [5]. In milder forms of the disorder where small amounts of circulating cytokines are present, it may be adequate to remove a portion of plasma and infuse "clean" plasma. This may serve to decrease the release of factors fueling the process. In more severe forms of the disorder, it may be necessary to suppress a patient's immune system to inhibit the generation of interleukins feeding the disease. Cyclosporine deserves more study in further cases of TTP refractory to conventional therapy.

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Sequence Analysis of HTLV-1 Provirus Associated With Adult T-Cell Leukemia/Lymphoma in Hong Kong

To the Editor: We have reported the first case of HTLV-1-associated adult T-cell leukemia/lymphoma (ATLL) in Hong Kong [1]. Now the sequence analysis of regions of *pX*, *pol*, and *env* (*gp21* and *gp46*) of the integrated provirus are discussed. The published sequences of these regions from Japanese prototype (ATK) and Papua New Guinea isolate (PNG-1) are also included for comparison (Fig. 1). The prototype ATK, an integrated provirus from a Japanese patient's leukemic cell, is the first to be completely sequenced [2]. PNG-1 is a newly characterized proviral clone from Papua New Guinea [3] and is thought to be evolutionally distinct from the prototype ATK.

High-molecular-weight DNA was extracted from the whole blood of the 42-year-old patient diagnosed with ATLL. The regions of interest were amplified by polymerase chain reaction (PCR). The PCR products were purified and sequenced directly with appropriate primers. The sequence of *pX* region amplified from our Hong Kong patient was virtually identical to published sequences of ATK and PNG-1. Since the open reading frame *pX* DNA encodes two important functional proteins, Tax and Rex, for viral expression and replication, the minimal sequence variation in this region among the HTLV-1 isolates is rather expected.

It is known that some regions within the *pol* gene are strongly conserved among different HTLV-1 clones because the protein it encodes is important in the retroviral life cycle. The sequence of the *pol* gene we amplified was identical to that of the published Japanese ATK but differed from the Papua New Guinea PNG-1 by 11 base-pairs. On the other hand, the sequence of the same region from PNG-1 varied by 9.3% from that of the prototype ATK [3].

The sequence similarity between the Japanese prototype ATK and the Hong Kong counterpart was also found in the *env* gene. The regions of the *env* gene we amplified included parts of *gp21* and *gp46* genes, which encode the transmembrane protein and the extracellular glycoprotein, respectively. The sequencing result of the amplified regions of the *gp21* and *gp46* gene showed a difference of only 5 and 3 base-pairs from those of the Japanese prototype ATK, whereas it showed a difference of 14 and 22 base-pairs from Papua New Guinea PNG-1.

The nucleotide sequence from our ATLL patient seemed more closely related to that of the Japanese. Furthermore, due to the geographic proximity and the fact that Hong Kong is not endemic of HTLV-1 infection, the integrated provirus from our Hong Kong patient might have originated from Japan.

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POL
CCTCCCTTGCTATTCGCCATAC*****************  HK
                                          ATK
                                          PNG-1

***********AGGACTTGTAGAACGCTCTAATGGCATT  HK
           --------------------------     ATK
           ---------G------------------   PNG-1

CTTAAAACCCTATTATATAAGTACTTTACTGACAAACCCG  HK
---------------------------------------  ATK
--------TT-----------------C----G----A   PNG-1

ACCTACCCATGGATAATGCTCTATCCATAGCCCTATGGAC  HK
---------------------------------------  ATK
-------T-----G-----------------T-------  PNG-1

AATCAACCAC**********************CAAAACC  HK
----------                                ATK
---T------                                PNG-1

CGATGCGAGCTTCACCAC                        HK

GP21
CAGTATGCTGCCCAGAACAGACG***********CCTGT  HK
                                    -----  ATK
                                    -----  PNG-1

TCTGGGAGCAAGGAGGATTATGCAAAGCATTACAAGAACA  HK
---------------------------------------  ATK
-------A-----------------G--GC---------G  PNG-1

GTGCTGTTTTCCGAATATTACTAATTCCCATGTCTCAATA  HK
----C----------------C-----------C-----  ATK
----T------TA--C--C--T--------CC--TT-----  PNG-1

TTACAAGAACGACCCCCCCTTGAGAATCGAGTCCTGACTG  HK
C--------A-------------------------------  ATK
-------------A---------------------------  PNG-1

GCTGGGGCCT**************CCTCTCACAGTGGGC  HK
----------                                ATK
--------T-                                PNG-1

TCGAG                                     HK

GP46
GGGTAAGTTTCTCGCCACTTTG*****************  HK
                                          ATK
                                          PNG-1

***CCCCTCATCTTCGGTGATTACAGCCCCAGCTGCTGTA  HK
   -----------------------------------   ATK
   -----AT---CA-T-C#------T-------------  PNG-1

CTCTCACAATTGGAGTCTCCTCATACCACTCTAAACCCTG  HK
---------------------------------------  ATK
-------T-----G---------------------------  PNG-1

CAATCCTGCCCAGCCAGTTTGTTCGTGGACCCTCGACCTG  HK
---------------------------------------  ATK
--------------------C--A--------T-----T  PNG-1

CTGGCCCTTTCAGCAGATCAGGCCCTACAGCCCCCCTGCC  HK
---------------------------------------  ATK
---------------------------------------  PNG-1

CTAACCTAGTAAGTTACTCCAGCTACCATGCCACCTATTC  HK
---------------------------------------  ATK
---GT-----G--C--------A------------------  PNG-1

CCTATATCTATTCCCTCATTGGATTAAAAAGCCAAACCGA  HK
----------------------C---G------------  ATK
------------------------T---A------------  PNG-1

AATGGCGGAGGCTATTATTCAGCCTCTTATTCAGACCCTT  HK
---------------------------------------  ATK
--------------C-----G--------------------  PNG-1

GTTCCTTAAAGAGCCCATACCTGGGGTGCCAATCATGGAC  HK
----------T-----------------------------  ATK
--------------------C---------------------  PNG-1

CTGCCCCTATACAGGAGCCGTCTCCAGCCCCTA         HK
--------                                  ATK
--------                                  PNG-1
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Fig. 1. Partial sequences of the amplified *pol*, *gp21*, and *gp46* regions. The published sequences of ATK and PNG-1 are aligned for comparison. The primer sequences for PCR and sequencing reaction are underlined. The region where the nucleotide sequence was not determined due to the sequencing limitation is indicated by an asterisk (*). A base deletion for the *gp46* of PNG-1 is represented by a number sign (#).