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COMPLETE RESPONSE TO RECOMBINANT ALPHA INTERFERON- 2b IN CLASSIC (AIDS NON-RELATED) KAPOSI'S SARCOMA AND AN UNUSUAL TOXICITY OF INTERFERON

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SUMMARY: A 63-year-old Turkish female with stage III generalized mucocutaneous nodular Kaposi's sarcoma which was not related to HIV infection was successfully treated with alpha interferon 2b, 5 million units/day subcutaneously. Complete disappearance of all measurable lesions were observed by the 4th week of therapy. However on the 6th week, the patient developed the symptoms of cardiac tamponade. One liter of pericardial effusion was drained. Biopsy and cytology were negative for the sarcoma involvement of the pericardium. Pericardial effusion was thought to be secondary to interferon therapy. Lesions recurred following discontinuation of interferon.
Key words: Interferon, Kaposi's sarcoma, pericardial effusion.

INTRODUCTION

Kaposi's sarcoma, first described by Moricz Kaposi as "idiopathic, multiple, pigmented sarcomas of the skin", eventually merged as a neoplasm bearing this dermatologist's name and was recognised as an unusual tumor primarily affecting the elderly males of Mediterranean or Ashkenazic Jewish origin (1). The natural history of Kaposi's sarcoma in the west, before the AIDS epidemic, has been well described. Occuring usually in the last part of the sixth of the seventh decade of life, the lesions appear on the lower extremities and occasionaly cause morbidity with development of extensive or confluent lesions. Another clinical form of Kaposi's sorcoma has been described among young black males in equatorial Africa. In this setting, the disease is often more agressive than is the Mediterranean form and early involmenet of lymph nodes an well as invasive cutaneous lesions are seen (2). Epidemic Kaposi's sarcoma is emerging as a frequently seen neoplasm in the United States and Europe because of its prevalance in AIDS patients.

Interferon alpha 2a and 2b appear to be efficacious agents in treating epidemic Kaposi's sarcoma; these agents cause regression of the neoplasm and may possibly have an antiretroviral effect against HIV (3,4,5,6). response rates varying from 30 % to greater than 50 % were obtained when high doses of interferon alpha was used in several trials of AIDS patients who do not had a proevious opportunistic infection (7). The rationale for using interferon in the treatment of this neoplasm included its properties as an immunomodulator, an antineoplastic agent, and an antiviral. We report herein a dramatic response to alpha interferon 2b in a classic form of Kaposi's sarcoma which was not AIDS associated.

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CASE PRESENTATION

63-year-old Turkish woman was admitted to the hospital for the evaluation of diarrhea, fever, abdominal cramps, dispnea and non-productive cough of two weeks duration. Past history revealed that she had had dark-purple, non-tender nodules on her lower extremities bilaterally for almost 6 months for which she had not sought a medical advise. Family and social history were not contributory.

Physical examination revealed that she had multiple, raised, red-purple, non-tender, non-pruritic nodules on her legs and thighs, as well as on her arms bilaterally (Fig. 1 and Fig. 2). She also had subdermal nodules and discolorations of the skin, suggesting bruise all over her anterior and posterior chest wall. Examination of the oropharynx also showed extensive lesions in the mucosa. Lymhadenopathy and organomegaly were not present. Biopsy of a lesion from the right thigh had shown sections of multiple capillaries with round or fusiform, proliferating neoplastic endotelial cells in the dermis. There were local condensations of hemosederin with erythrocytes and lymphocytes appearing in the tissue. The pathological diagnosis was Kaposi's sarcoma (Fig. 3). Panendoscopic examination of the gastrointestinal tract and computerized axial tomography of the chest did not disclose similar lesions in the gastrointestinal tract and in the lung, respectively. Other viscera, bone and bone marrow were proven to be intact. HTLV III test was repeatedly negative.

The patients was put on weekly vinblastine 6 mg/m2, iv. regimen with titrated WBC count above 2.500 cells/ml. A partial responce was obtained in 3 weeks with regression of most of the lesions and disease stabilization in the rest. However the follow up of the patients was not possible due to unattandance to outpatients visits for the ensuing 4 months.

Four months later the patients presented with disseminated cutaneous manifestatons of the disaase. The lesions were progressed and coalesced, developing into large fungating lesions in the lower extremities. There was also massive lymphedema of the left thigh and leg due to obstruction of the lymphatic drainage. She was treated with vinblastine, 4 mg/m2 intravenously alternating weekly with bleomycine, 15 U/m2 intravenously. This caused profound neutropenia although partial regression of the lesions was observed.

After recovery of the prolonged myelosupression she was started on alpha-2 interferon 2b (Intron-A) 5 million units/ day subcutaneously. In 4 weeks complete regression of all the measurable lesions was observed in addition to the resolution of the lymphedema of the left thigh and leg. She was kept on daily interferon treatment.

On the 6th week of interferon treatment the patients developed orthopnea. Physical examination revealed percussion dullness beyond the 5 th intercostal space at the left midclavicular line; jugular veins appeared distended. The paradoxic pulse was also pronounced. Serial electrocardiogrophic examination demonstrated ST-segment elevation without reciprocal depression. Chest x-rays and cardiac fluoroscopy studies were suggestive of pericardial effusion. Echocardiogrophy demonstrated extensive pericardial effusion (Fig. 4 and Fig. 5).

Blood chemistry and CBC work up revealed following results; ESR: 22 mm/hr, RBC: 2.500.000 /mkL, WBC: 6.800 /mkL, fasting blood sugar: 96 mg/dL, alkaline phosphatase 26 U/dL, SGOT: 12 U/dL, SGPT: 10 U/dL, Bilirubins Direct: 0.1 mg/dL, indirect: 0.4 mg/dL, uric acid: 4.3 mg/dL, creatinine: 0.8 mg/dL total protein: 5.3 mg/dL, albumine: 3 gr/dL, gamma GT: 15 U, LDH: 375 U/L, amylase: 122 sU/dL, T1U: 25.0 % , TT4: 4.5 mkg/dL, TSH: 4 mkIU/ml, FTI: 1.2, LE: (-), anti-DNA: (-), RF: (-), HTLV-III: (-), HTLV-I: (-), EB: (-), mono spot test: (-), total T-cells: 72 %, supressor T-cells: 28 %, helper T-celles: 54 %, Candida skin test: (-), DNCB: (-).

Needle aspiration of the pericardial sac was performed and 850 ml of serous effusion was drained. The chest X-ray after the drainage is shown in Fig. 6. Biochemical examination of the fluid revealed protein: 1.7 gr/dL, LDH: 198 U/L, and cholesterol: 22 mg/dL. cy-

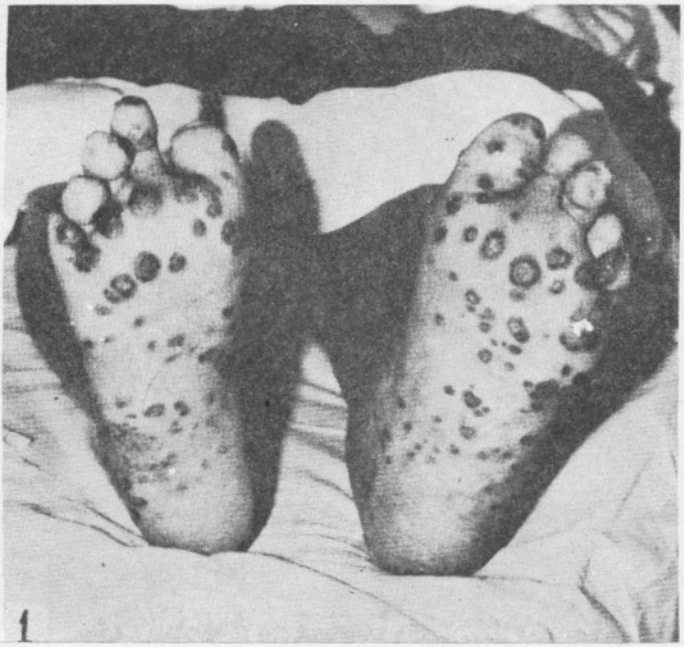
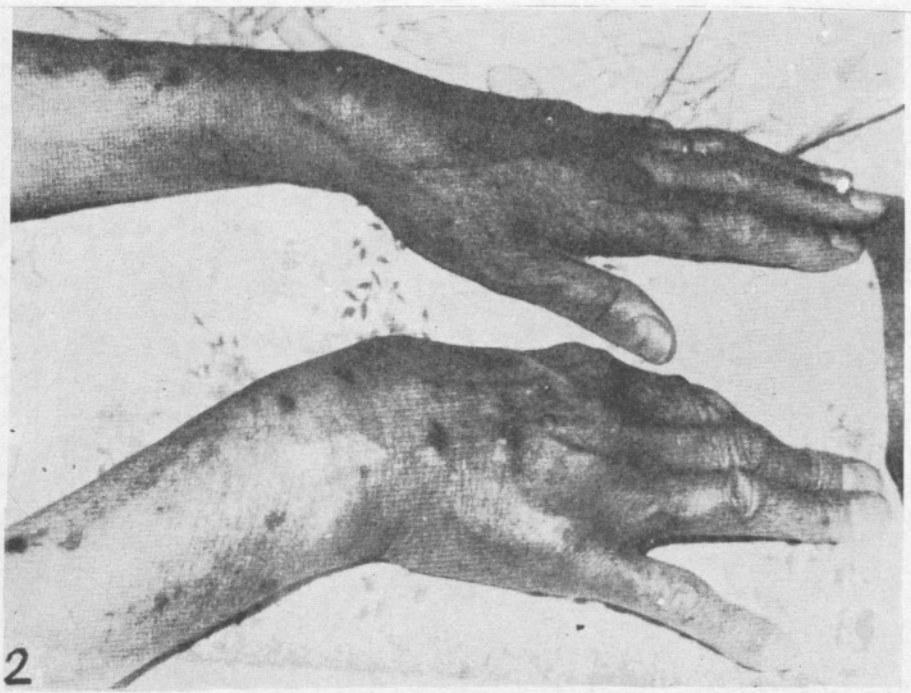


FIG. 1 and FIG.2: Physical examination of the patient revealed that she had multiple, raised, nontender, red-purple, non-pruritic nodules on her legs and thighs as well as on her arms bilaterally.



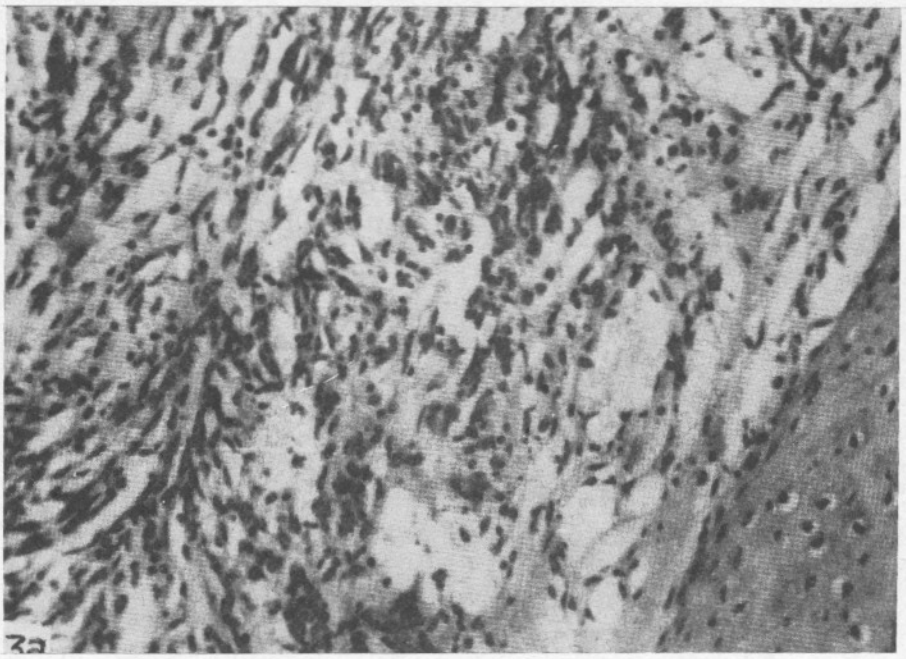
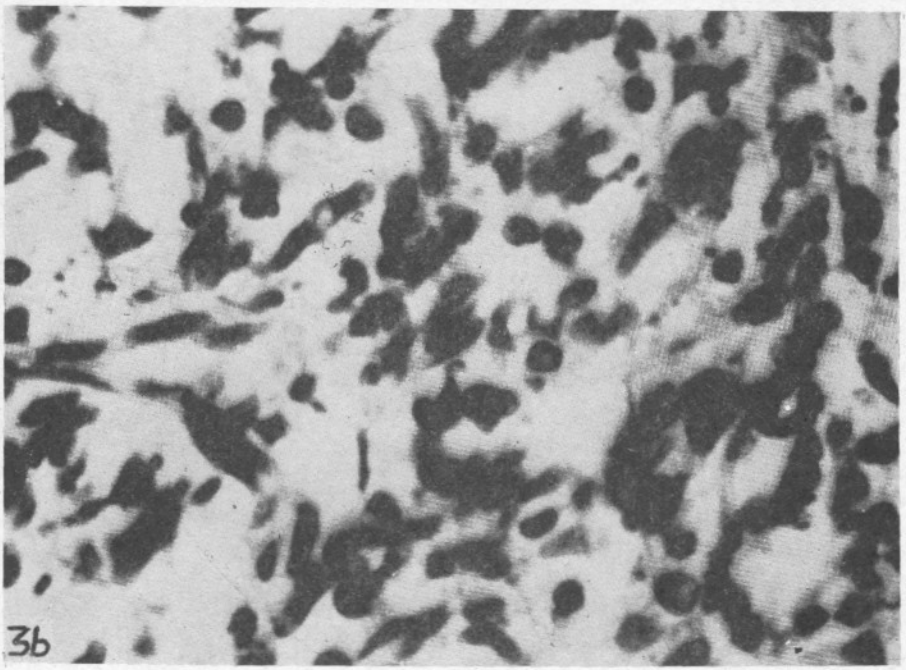


FIG. 3a (x 40) and b (x 100): In the pathological examination of the biopsy of a lesion, sections of multiple capillaries with round or fusiform, proliferating neoplastic endothelial cells in the dermis were seen. Note the local condensations of hemosiderin with erythrocytes and leucoytes appearing in the tissue.



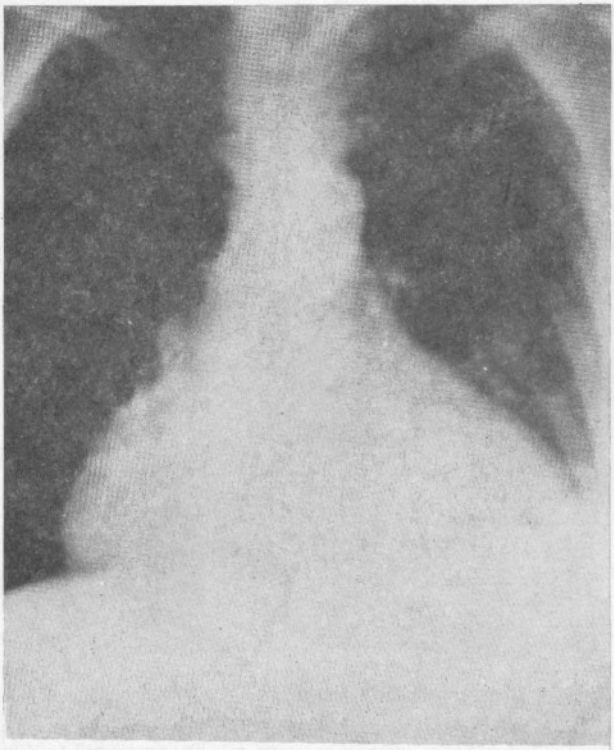
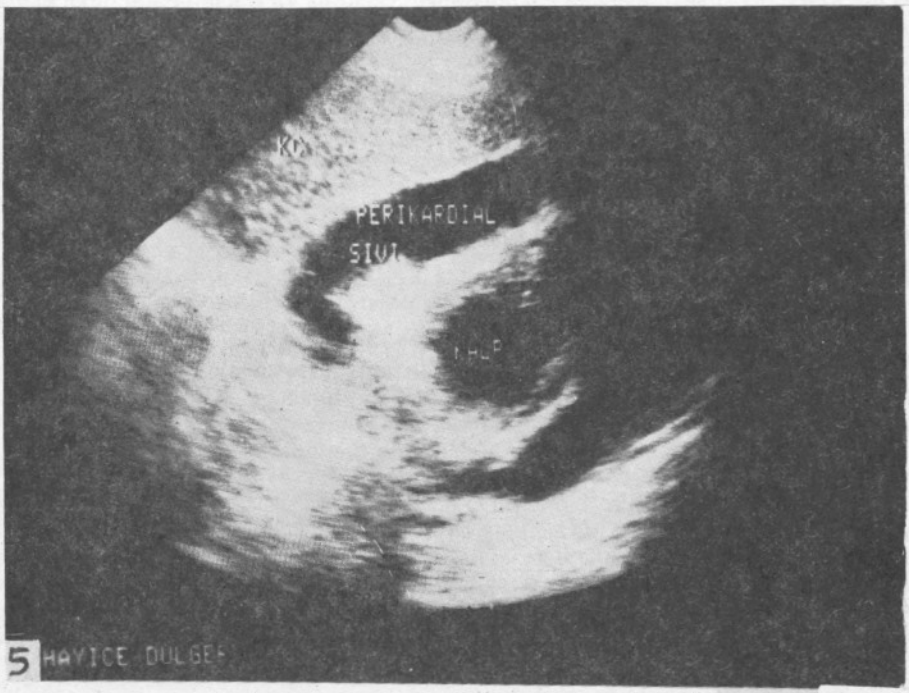


FIG. 4: Chest X-ray and FIG. 5: Echocardiograph of the patient demonstrating extensive pericardial effusion.



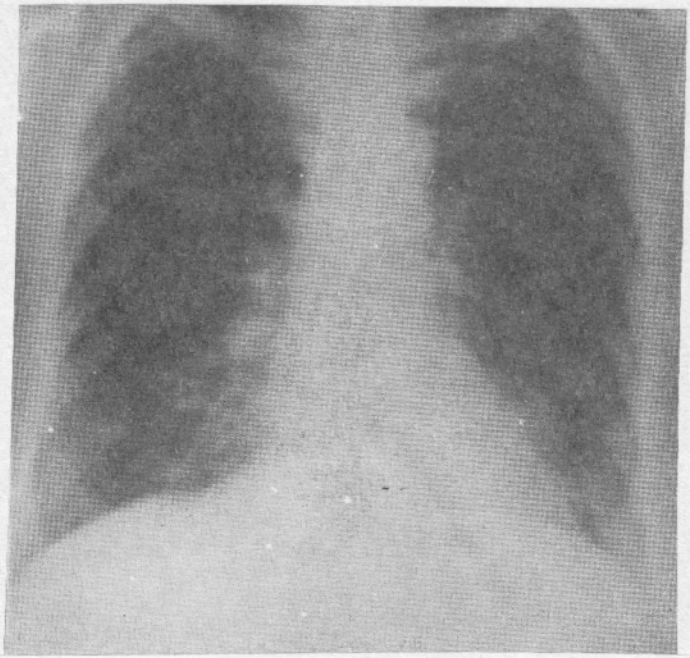


FİG. 6: Chest X-ray of the patient, after the pericardial drainage.

topathologic examination of the fluid confirmed normal mesothelial cells. Tubercle bacilli was not found. PPD skin test was also negative. Cultures for bacteria and fungi did not demonstrate a pathologic growth.

Removal of the fluid relieved the tamponade. However 8 days later pericardial fluid reaccumulated and signs of recurrent tamponade became manifested. Interferon was discontinued at this stage. Surgical drainage of 980 ml. of serous pericardial fluid was performed along with an open biopsy of the pericardium. Pathological examination of the biopsy specimen did not demonstrate sarcoma involvement. Serial echocardiographic examinations failed to show any valvular lesions.

Upon discontinuation of interferon pericardial effusion did not recur. Nodular lesions of the sarcoma, however, reappeared in two weeks.

DISCUSSION

Recombinant and natural interferons have been extensively studied in epidemic Kaposi's sarcoma (8,9). The interferons had been recognized to augment T-cell mediated cytotoxicity, NK cell activity, and certain macrophage functions. The results of various trials with different, highly purified alpha interferon species, including recominant interferon alpha-2a, recombinant interferon alpha-2b and interferon alpha N1 have consistently ranged between 25 % and 40 % objective response (10).

The mechanism of action of interferon in epidemic Kaposi's sarcoma is still controversial. It may be antineoplastic, as suggested by the significantly higher response rate with higher doses of drugs. Nonetheless, it is also possible that the antiviral effect of interferon on HIV requires such higher doses. It is not known whether interferon supresses HIV replication in vivo in patients with Kaposi's sarcoma. It has been difficult to accurately assess viral activity in patients (11). Nevertheless, periliminary studise have dem-

onstrated that patients in complete remissions of interferon alpha became virus culture negative; with subsequent discontinuation of treatment, cultures turned positive (12). There has not ben a clearly discernible immunologic effect in Kaposi's sarcoma patients treated with interferons (13).

In classi Kaposi's sarcoma, a fairly uniform response rate of 90 to 95 % was observed with vinca alkaloids, partucilarly viblastine. Several trials using combination chemotherapy, particularly bleomycine, BCNU, vinca alkaloids, actinomycin D and DTIC, confirmed the chemoresponsiveness of Kaposi's sarcoma. Most of these combinations are well tolerated and produced high response rates (14). Contrary to the chemosensitivity to cytotoxic drugs, AIDS non-related classic Kaposi's sarcoma was not proven to be inresponsive to alpha interferon. Reports of complete responses to alpha interferon in AIDS non-associated Kaposi's sarcoma are scarce in Turkey (15). The efficacy of alpha interferon 2b in our case could be either due to its immunomodulator activity or the antineoplastic property. The latter seems to be more likely, due to the intact cellular immunity in this case, prior to therapy, as well as during and after the interferon therapy, reflected by skin tests and T-cell subpopulation studies.

Another interesting aspect of our case is the development of recurrent massive pericardial effusion which was concluded to be interferon associated. Although borderline thyroid function tests may reflect insidious underlying hypothyroidism, immediate relief of smptoms and non-recurrence of pericardial effusion after discontinuation of interferon, strongly support our suggestion. All other causative factors including the sarcoma involvement of the percardium has been carefully eliminated.

REFERENCES

1. Centers for Disease Control: Kaposi's sarcoma and pneumocystis pneumonia, among homosexual men. New York City and California. MMWR 30: 305, 1981.
2. Groopman, J.E.: Biology and Therapy of Epidemic Kaposi's sarcoma. Cancer 59: 633-637, 1987.
3. Groopman, J.E.; Gottleib, M.S.: Recombinant alpha-2 interferon Therapy of Kaposi's sarcoma associated with Immune Deficiency Syndrome. Ann. Int. Med., 100: 671-676, 1984.
4. Mitsuyasu, R.T.: Biology and Therapy of Kaposi's sarcoma. Semi. Oncol., 11: 53-59, 1984.
5. Mitsuyasu, R.T.; Volberding, P.A.: High dose alpha-2 interferon in the therapy of Epidemic Kaposi's sarcoma in AIDS. Proc. Am. Cos. Clin. Oncol., 3: 51, 1984.
6. Krown, S.E.; Real, F.X.: Preliminary Observations on the effets of recombinant Leukocyte A interferon in Homosexual men with Kaposi's sarocma. N. Eng. J. Med. 308: 1071-1076, 1986.
7. Raj. S.; Wong, G.: Immunological variables as Predictors of prognosis in Patients with Kaposi's sarcoma and the AIDS. Cancer Res., 46: 417-425, 1986.
8. Groopman, J.E.; Broder, S.: Cancer in AIDS and other immunodeficiency states. In: De Vita, V.T.: Cancer, Prinicples and Practice of Oncology. 3rd Ed., J.B. Lippincot Co., Philadelphia, 1989.
9. Rios, A.; Mansel, P.W.A.: Treatment of Acquired Immunodeficiecy Syndrome-related Kaposi's sarcoma with lymphoblastoid interferon. J. Clin. Oncol. 3: 506, 1985.
10. Krown, S.E.: Recombinant Leukocyte A interferon in Kaposi's sarcoma. Ann. N.Y. Acad. Sci. 437: 431, 1984.
11. Vadhan-Raj, S.; Al-Katip, A.: Phase 1 trial of recombanant iterferon Gamma in Cancer Patients. J. Clin Oncal. 4: 137, 1986.
12. Volberding, P.A.: Alpha interferon Therapy of Kaposi's sarcoma in AIDS. Ann. N.Y. Acad. Sci. 437: 439, 1984.
13. Fischl, M.: Intereron alpha-N1 wellferon in Kaposi's sarcoma. Single agent of combination with vinblastine (abstr.). J. Interferon Res. 6 (Suppl. 1): 4, 1986.
14. Glaspy, J. Miles, S.: Treatment of advanced stage Kaposi's sarcoma with vincristine and bleomycine (abstr.). Proc. Am. Soc. Clin. Oncol. 5: 3, 1986.
15. Ferhanoglu, B.; Dobrucalı, A,: Tabak, F. et. al: Kaposi's sarcoma and interferon. 21st National Congress of Hematology and 1st National Congress of Chemotherapy. 11-14 October 1989. İstanbul, Turkey.