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Letters

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Type C Hepatitis and Chronic Lymphocytic Leukaemia

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CHRONIC lymphocytic leukaemia (CLL), characterised by monoclonal proliferation of small B lymphocytes, represents a frequent disorder of the elderly [1]. Although the cause of this malignancy is still unknown, a large body of pathogenetic mechanisms, including genetic and/or environmental and/or viral agents, have been suggested [2]. CLL shares clinico-epidemiological characteristics with other benign or malignant B-cell disorders such as type II mixed cryoglobulinaemia (MC) [3] and B-cell non-Hodgkin's lymphoma (NHL), respectively. These diseases share some immunological manifestations, such as Sjögren's syndrome, rheumatoid arthritis, thyroiditis, hypo- or hyperglobulinaemia, with or without cryoglobulinaemia. In addition to the clinico-serological overlap, it is possible to observe the evolution from one disorder to another during the natural course of these diseases [2, 4]. In the last 5 years, an interesting association between hepatitis C virus (HCV), an hepatotropic and lymphotropic virus [5], and MC, has been demonstrated [4, 6]. Moreover, HCV infection of peripheral blood mononuclear cells (PBMC) from MC patients suggests a role of HCV in the B-cell proliferation, which underlies the disease [7], that in some subjects can evolve to a frank NHL [4, 8]. More recently, the detection of HCV infection in a third of 'idiopathic' B-cell NHL raised the hypothesis that HCV could also be involved in the oncogenesis of such lymphomas [9]. Here we report the clinical characteristics of two patients with type C chronic hepatitis complicated by CLL after a follow-up period of 12 and 25 years, respectively (Table 1). Patients were Italian-born heterosexuals and had no history of blood transfusions or alcohol abuse, nor had either received interferon or immunosuppressive treatment. The diagnosis of CLL was made according to current criteria [1, 2] and in one patient [no. 2] by bone marrow biopsy evaluation.

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Table 1. Patients' characteristics

	Patient 1	Patient 2
Age/sex	75/M	77/F
Sjögren's syndrome	+	+
Peripheral neuropathy	–	+
Mixed cryoglobulinaemia (IgG–IgMk)	–	+
Liver involvement duration (yrs)	14	26
CLL duration (yrs)	2	1
Anti-HCV (RIBA II)	+	+
HCV RNA serum (PCR+)	+	+
HCV RNA in PBMCs	+	+

RIBA: radio-immune-based assay; PCR: polymerase chain-reaction technique.

The presence in the serum of both antibodies against HCV and HCV RNA was demonstrated by RIBA II (Chiron, Emeryville, California, U.S.A.) and 'one-tube' nested PCR [7], respectively (Table 1). In addition, HCV genomic sequences were also detected in fresh and cultured PBMC. Exposure to other lymphotropic viruses, i.e. EBV, HIV and HBV, was not detected.

The clinical course and the virological findings of these two subjects suggest the possible pathogenetic role of HCV infection in some CLL, similar to previous observations regarding 'idiopathic' NHL as well as NHL-complicating MC or type C hepatitis [8–10]. The oncogenesis of CLL is probably a multifactorial pathological process in which chronic HCV infection could induce the reactivation of other viral agents, such as silent herpes virus, or the expression of particular oncogenes [2]. However, due to the different geographical distribution of HCV infection, the frequency of CLL-complicating type C hepatitis could be extremely variable among patient populations from different countries. Finally, the possible role of HCV infection on CLL could indirectly explain the positive effect of interferon treatment alone or in combination with chemotherapy in a subset of CLL patients [2, 11].

1. Finch SC, Linet MS. Chronic leukaemias. *Baillieres Clin Haematol* 1992, **5**, 27–56.
2. Rozman C, Montserrat E. Chronic lymphocytic leukemia (review). *N Engl J Med* 1995, **333**, 1052–1057.
3. Gorevic PD, Frangione B. Mixed cryoglobulinemia cross-reactive idiotypes: implication for relationship of MC to rheumatic and lymphoproliferative diseases. *Semin Hematol* 1991, **28**, 79–94.
4. Ferri C, Zignego AL, Bombardieri S, *et al.* Etiopathogenetic role of hepatitis C virus in mixed cryoglobulinemia, chronic liver diseases and lymphomas. *Clin Exp Rheumatol* 1996, **13** (Suppl. 13), S135–S140.
5. Zignego AL, Macchia D, Monti M, *et al.* Infection of peripheral mononuclear blood cells by hepatitis C virus. *J Hepatol* 1992, **15**, 382–386.
6. Ferri C, Greco F, Longombardo G, *et al.* Hepatitis C virus antibodies in mixed cryoglobulinemia patients. *Arthritis Rheum* 1991, **34**, 1606–1610.
7. Ferri C, Monti M, La Civita L, *et al.* Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia. *Blood* 1993, **82**, 3701–3704.
8. La Civita L, Zignego AL, Monti M, Longombardo G, Pasero G, Ferri C. Mixed cryoglobulinemia as a possible preneoplastic disorder. *Arthritis Rheum* 1995, **38**, 1859–1860.
9. Ferri C, Caracciolo F, La Civita L, *et al.* Hepatitis C virus

infection and B-cell lymphomas. *Eur J Cancer* 1994, **30A**, 1591–1592.
10. Ferri C, La Civita L, Monti M, *et al.* Can type C hepatitis be complicated by B-cell malignant lymphoma? *Lancet* 1995, **346**, 1426–1427.
11. Montserrat E, Villamor N, Urbano-Ispizua A, Ribera JM, Rozman C. Alpha interferon in chronic lymphocytic leukaemia. *Eur J Cancer* 1991, 27(Suppl. 4), S74–S77.

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Angiosarcoma of the Breast After Conservative Surgery and Radiation Therapy for Breast Carcinoma: Three New Cases

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We report 3 cases of breast angiosarcoma which arose in patients who had received conservative treatment including radiation for adenocarcinoma of the breast.

Patient 1

A 59-year old woman presented with two tumours (measuring 7.5 cm and 1.5 cm) in her left breast. The patient has been treated 4 years previously for a pT2pN0 medullary carcinoma of the same breast. After lumpectomy, 45 Gy was delivered to the whole breast, followed by a boost of 15 Gy to the tumour bed. The mastectomy specimen showed a bifocal grade III angiosarcoma [1]. Nine months after simple mastectomy, the patient experienced spinal and pulmonary metastases and a left chest wall recurrence. Chemotherapy did not prevent progression. The patient died 14 months after mastectomy.

Patient 2

A 49-year old woman presented with an inflammatory and ecchymotic infiltration (18 × 15 cm) in the her left breast. The patient had been treated 6.5 years previously by lumpectomy and radiation (doses unknown) for a pT1pN0 carcinoma of the same breast. The mastectomy specimen revealed a multifocal grade I angiosarcoma of the skin infiltrating the underlying parenchyma. Four months after simple mastectomy, the patient experienced a local recurrence. Despite chemotherapy, she died of regional disease progression 19 months after the mastectomy.

Patient 3

A 66-year old woman presented with a violaceous tumour (3.5 × 3 cm) in the nipple of her left breast. The patient had been treated 4.5 years previously for a pT1pN0 carcinoma of the same breast. After lumpectomy, 45 Gy was delivered to the whole breast, followed by a boost of 15 Gy to the tumour bed. The biopsy of the nipple tumour disclosed a multifocal grade II angiosarcoma. Eighteen months after simple mastectomy, there is no evidence of disease.

Including the cases from the Gustave-Roussy Institute, 33 cases of angiosarcoma diagnosed in a breast previously treated by conservative surgery and radiation for carcinoma have been reported [2–10]. Angiosarcoma developed 29–150 months (mean: 66 months) after the local treatment of the adenocarcinoma. Radiation doses to the whole breast ranged from 40–56 Gy (30 patients). A boost to the tumour bed (10–25 Gy) was delivered in 24 cases. Seven sarcomas were grade III, 4 grade II and 6 grade I. The local treatment was a total mastectomy in all but 4 patients. Tumour recurred locally in 15 cases, with a mean interval of 8 months. After a mean follow-up time of 18 months, 10 patients (out of 28) had died. So far, angiosarcomas arising in a breast treated by radiation are similar to those arising in a previously healthy breast.

These cases raise the question whether radiation therapy may 'induce' angiosarcoma in the irradiated breast. To confirm this hypothesis, it would be necessary to show (by a case–control study) that the radiation therapy of the patients who develop angiosarcoma after conservative treatment for carcinoma was in some way different from the radiation therapy of similarly treated patients who have no angiosarcoma after a comparable time of follow-up.

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1. Trojani M, Contesso G, Coindre JM, *et al.* Soft tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. *Int J Cancer* 1984, **33**, 37–42.
2. Wijnmaalen A, Van Ooijen B, Van Geel BN, Henzen-Logmans SC, Treurniet-Donker AD. Angiosarcoma of the breast following lumpectomy, axillary lymph node dissection, and radiotherapy for primary breast cancer: three case reports and a review of the literature. *Int J Radiat Oncol Biol Phys* 1993, **26**, 125–139.
3. Bonetta A, Pagliari C, Morrica B. Post-radiation angiosarcoma of the breast: a clinical case. *Tumori* 1995, **81**, 219–221.
4. Del Mastro L, Garrone O, Guenzi M, *et al.* Angiosarcoma of the residual breast after conservative surgery and radiotherapy for primary carcinoma. *Ann Oncol* 1994, **5**, 163–165.
5. Fineberg S, Rosen PP. Cutaneous angiosarcoma and atypical vascular lesions of the skin and breast after radiation therapy for breast carcinoma. *Am J Clin Pathol* 1994, **102**, 757–763.
6. Provencio M, Bonilla F, Espana P. Breast angiosarcoma after radiation therapy. *Acta Oncol* 1995, **34**, 969.
7. Rasinariu A, Sabourin JC, Calitchi E, Feuilhade F. Angiosarcome du sein. A propos d'un cas apparu 5 ans après radiothérapie pour cancer du sein. *Cah Oncol* 1994, **3**, 159–162.
8. Slotman BJ, van Hattum AH, Meyer S, Njo KH, Karim ABMF. Angiosarcoma of the breast following conserving treatment for breast cancer. *Eur J Cancer* 1994, **30A**, 416–417.
9. Weber B, Marchal C. Three cases of breast angiosarcomas after breast-conserving treatment for carcinoma. *Radiother Oncol* 1995, **37**, 250–252.
10. Zucali R, Merson M, Placucci M, Di Palma S, Veronesi U. Soft tissue sarcoma of the breast after conservative surgery and irradiation for early mammary cancer. *Radiother Oncol* 1994, **30**, 271–273.