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Primary non-Hodgkin lymphoma of the liver and asbestos exposure

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Summary. A 42-year-old man was diagnosed with a Bcell, centroblastic, follicular non-Hodgkin lymphoma of the liver in 1992. He had worked as carpenter and shipwright in various firms and as a fitter at the Monfalcone shipyards. Partial hepatectomy and chemotherapy were performed. The patient remained symptom-free for 14 years. In 2006 lymphoma recurred with involvment of left subpleural tissue, some ribs, abdominal and pelvic lymphnodes. Chemotherapy resulted in a transitory improvement. The patient died in 2008. In this case, occupational history indicates that the patient had heavily exposed to asbestos. Asbestos, as an agent inducing immune impairment, plausibly played a major role in the development of liver lymphoma as well as in the recurrence of the disease.

Key words: non-Hodgkin lymphoma, extranodal lymphoma, liver, asbestos, immune impairment

Introduction

Numerous studies have illustrated different aspects of the primary hepatic lymphomas (1-4). Factors indicated as plausibly relevant in the etiology of this rare condition include viruses (hepatitis B, hepatitis C, Epstein-Barr), persistent inflammatory processes associated with hepatitis C virus infection or autoimmune disease (4). However, the causes of hepatic non-Hodgkin lymphoma as well as those of non-Hodkgin lymphoma in general remain poorly known. We report a case of hepatic non-Hodgkin lymphoma, developed in a person with a history of severe exposure to asbestos, and we discuss the possible relationship between non-Hodgkin lymphoma and asbestos.

Case report

A 42-year-old man began to complain of bloated feeling in April 1992. Five months later abdominal ultrasonography and CT revealed a mass in the left lobe of the liver. Non-Hodgkin lymphoma was diagnosed at the biopsy. In October 1992 the patient was admitted to an University Hospital. Serology was negative for B and C hepatitis. At the CT a solid mass, cm 8x12 in diameter, was found in the left lobe of the liver. The biopsy showed a B cell, centroblastic, follicular non-Hodgkin lymphoma. Bone marrow biopsy was negative. In November 1992 partial resection of the liver and cholecystectomy were performed. The patient was then treated by chemotherapy (six cycles F-MACHOP), and one year later with re-infusion of autologous staminal cells. He remained asymptomatic for a 14-year period. In June 2006 he complained of pain at the left lumbar region. In the following months he noted weight loss. In September 2006 a total PET CT showed a large thickening of the subpleural tissue in the left paravertebral area; the lesion extended to the posterior portion of the 10th and 11th ribs with suspected involvement of the vertebrae. In addition, numerous abdominal and pelvic foci were seen, the largest of them located at the left hypocondrion; right periiliac and perifemoral lymphoadenopaties coexisted. Biopsy of obturatorial and iliac lymphnodes showed a follicular non-Hodgkin lymphoma degree

2, CD3-, CD10+, CD20+, bc12+, bc16+, Cyclin D1-. The patient was treated by chemotherapy (ESHAP and Rituximab). A reduction of the tumoral masses was documented and bone marrow transplantation was performed. An improvement in the general conditions was obtained. In October 2007 CT showed a worsening. Chemotherapy was carried out and severe leucopenia occurred. The general conditions showed a progressive deterioration and the patient died in March 2008.

The patient had worked as carpenter and shipwright in various firms in the Monfalcone area for nine years (1966-1975). Successively, he had worked as a fitter at the Monfalcone shipyards for 17 years (1976-1993).

Discussion

In the current case the disease showed a biphasic course. In the first phase the treatment was strongly efficacious, resulting in a long disease-free period. Nevertheless, after 14 years, lymphoma, again follicular in pattern, recurred and led the patient to death in less than two years.

The patient had worked for many years as a fitter in the shipyards of Monfalcone. It is well known that in the past heavy exposure to asbestos occurred in shipbuilding. As far as the Monfalcone shipyards are regarded, a number of investigations have demonstrated that exposure involved all people working in this plant (5).

Asbestos is well recognized as a cancerogenic agent. However, the entire spectrum of asbestos oncogenic effects is not defined. The role of asbestos in the genesis of some tumors, such as mesotheliomas of pleura, pericardium, peritoneum, lung carcinoma, larynx carcinoma, ovary carcinoma, is ascertained. In addition, various data suggest that asbestos might cause or favour cancer at other sites (gastrointestinal tract, oropharynx…) (6).

The relationship between asbestos and hematopoietic neoplasms have been explored since some 50 years. In 1966 Lieben (7), by examining 68 cases of pulmonary asbestosis, observed 21 malignancies; these included lymphocytic leukemia (two cases), acute leukemia (one case), lymphoblastoma (one case), multiple myeloma (one case). In 1970 Gerber (8), by examining at necropsy 35 cases of pulmonary asbestosis, found two cases of multiple myeloma, two cases of myeloproliferative disorders, and one case of Waldenström macroglobulinemia. Gerber concluded that the incidence of hemopoietic tumors was significantly higher among asbestosis people than among non-asbestosis subjects. In 1982 a case-control study showed an excess of non-Hodgkin lymphomas arising in the gastrointestinal tract and in oral cavity among people exposed to asbestos (9). In addition, numerous cases have been reported in which asbestos-related lesions were associated to lymphomas or to other lymphoproliferative lesions (10-16). In a study regarding a small group of workers exposed to asbestos, a very rare condition was found, namely an intraperitoneal non-Hodgkin lymphoma (17). At the Monfalcone Hospital in a series of 169 pleural mesotheliomas, esamined at necropsy, mesothelioma was associated to a non-Hodgkin lymphoma in three cases; in two of these, lymphoma was extranodal, having been developed in the liver and in the brain respectively (18). The patient with pleural mesotelioma and liver lymphoma had worked in shipbuilding and showed a very high number of asbestos bodies in the lung tissue (130,000 bodies per gram of dried tissue). Moreover, in the Trieste-Monfalcone area various cases of lymphoma have been described in people heavily exposed to asbestos (19-25).

In a review of the epidemiological literature on asbestos and malignant lymphomas, Becker et. al (26) concluded that taken as a whole, available epidemiological data indicated a higher risk of lymphomas after asbestos exposure. More recent studies gave conflicting results (27-29). The epidemiological studies on this issue are difficult to interpret. The label non-Hodgkin lymphoma covers somewhat heterogeneous entities. It has been observed that the risks under study could exist only for some types of lymphomas and not for lymphomas in general or that such risks are of different magnitude for the different lymphoma types (30). In evaluating the relationship asbestos-lymphomas the criterion of biological plausibility should also be considered. Among the known etiological factors in the genesis of non-Hodgkin lymphomas, the most relevant one is represented by the immunodeficiency.

When the immune defence is impaired, the incidence of non-Hodgkin lymphoma strongly increases. This is observed in the course of HIV-AIDS as well as among immunosoppressed transplant recipients (31). On the other hand it is well known that asbestos may induce relevant changes of immune system. Such changes have been object of various studies (32-34).

Available data about the etiology of non-Hodgkin lymphomas and about asbestos effects on immune system suggest the existence of an etiological relationship between asbestos and lymphomas in general. Moreover, the plausibility of such a relationship becomes higher in the case of extra-nodal lymphomas. In fact, just this variety of lymphomas, very rare in the general population, becomes very frequent among people with immune impairment.

Finally, in the present case the immune impairment induced by asbestos could also explain why, after an early longtime favourable course, lymphoma has relapsed.

References

1. Page RD, Romaguera JE, Osborne B, *et al.* Primary hepatic lymphoma: favorable out come after combination chemotherapy. Cancer 2001; 92: 2023-9.
2. Agmon-Levin N, Berger I, Shtalrid M, *et al.* Primary hepatic lymphoma: a case report and review of the literature. Age Ageing 2004; 33: 637-40.
3. Masood A, Kairouz S, Hudhud KH, *et al.* Primary non-Hodgkin lymphoma of liver. Curr Oncol 2009; 16: 74-7.
4. Kikuma K, Watanabe J, Oshiro Y, *et al.* Etiological factors in primary hepatic B-cell lymphoma. Virchows Arch 2012; 460: 379-87.
5. Bianchi C, Brollo A, Ramani L. Asbestos exposure in a shipyard area, Northeastern Italy. Ind Health 2000; 38: 301-8.
6. IARC: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. A review of Human carcinogens: Metals, arsenic, dusts, and fibres, Lyon, WHO, IARC 2012; 100 C.
7. Lieben J. Malignancies in asbestos workers. Arch Environ Health 1966; 13: 619-21.
8. Gerber MA. Asbestosis and neoplastic disorders of the hematopoietic system. Am J Clin Path 1970; 53: 204-8.
9. Ross R, Dworsky R, Nichols P, *et al.* Asbestos exposure and lymphomas of the gastrointestinal tract and oral cavity. Lancet 1982; 2: 1118-20.
10. Kagan E, Jacobson RJ. Lymphoid and plasma cell malignancies: asbestos-related disorders of long latency. Am J Clin Pathol 1983; 80: 14-20.
11. Parisio E, Bianchi C, Rovei R, *et al.* Pulmonary asbestosis associated to pleural non-Hodgkin lymphoma. Tumori 1999; 85: 75-7.
12. Mizuno S, Ota S, Tanaka T, *et al.* Primary tracheal malignant lymphoma detected during a regular checkup in an asbestos dust-exposed smoker. Acta Med Okayama 2014; 68: 177-81.
13. Longo MS, Giordano D, Papa D, *et al.* Su di un caso di associazione mesotelioma IgG-mieloma. Rivista Ospedale Sampierdarena 1983; 21: 29-38.
14. Efremidis AP, Waxman JS, Chahinian AP. Association of lymphocytic neoplasia and mesothelioma. Cancer 1985; 55: 1056-9.
15. Hayashi Y, Mizuo K, Hayashi K. An autopsy case of double cancer of multiple myeloma and malignant mesothelioma (in Japanese). J Jpn Soc Intern Med 1989; 78, 1611-2.
16. Li X, Brownlee NA, Sporn TA, *et al.* Malignant (diffuse) mesothelioma in patients with hematologic malignancies: A clinicopathologic study of 45 cases. Arch Pathol Lab Med 2015;139:1129-36.
17. Oksa P, Pukkala E, Karjalainen A, *et al.* Cancer incidence and mortality among Finnish asbestos sprayers and in asbestosis and silicosis patients. Am J Ind Med 1997; 31: 693-8.
18. Bianchi C, Bianchi T, Ramani L. Malignant mesothelioma of the pleura and other malignancies in the same patient. Tumori 2007; 93: 19-22.
19. Bianchi C, Di Bonito L, Brollo A, *et al.* Primary lymphoma of the brain and asbestosis (abstract). Acta Neurologica 1983; 5: 308.
20. Bianchi C, Brollo A, Bittesini L. Esposizione all'asbesto e linfomi non-Hodgkin nel territorio di Monfalcone. In: Furbetta D, Abbritti G (a cura di), 47° Congresso della Società Italiana di Medicina del Lavoro e Igiene Industriale, Monduzzi Editore, Bologna 1984; 1077-80.
21. Bianchi C, Bianchi T, Bucconi S. Non-Hodgkin lymphoma of the testis and malignant mesothelioma of the pleura in the same patient. Eur J Oncol 2010; 15: 167-71.
22. Bianchi C, Bianchi T. Asbestosis, lung adenocarcinoma with lymphocytic infiltration, and non-Hodgkin lymphoma. Eur J Oncol 2015; 20: 193-8.
23. Bianchi C, Bianchi T. Linfoma non Hodgkin ed esposizione all'asbesto (Lettera). Med Lav 2015; 107: 73-4.
24. Bianchi C, Bianchi T. Non-Hodgkin lymphoma and pleural mesothelioma in a person exposed to asbestos. Turkish J Pathol 2015; DOI: http://dx.doi.org/10.5146/tjpath.2015.01332. Disponibile su: <http://www.turkjpath.org/text.php3?id=1771>.
25. Bianchi C, Bianchi T. The possible role of asbestos exposure in the pathogenesis of a thoracic non-Hodgkin lymphoma (Letter). Arch Bronconeumol 2016; DOI: http://dx.doi.org/10.1016/j.arbres.2016.01.016.
26. Becker N, Berger J, Bolm-Audorff U. Asbestos exposure and malignant lymphomas – a review of the epidemiological literature. Int Arch Occup Environ Health 2001; 74: 459-69.
27. Weisenburger DD, Chiu BC. Does asbestos exposure cause non-Hodgkin's lymphoma or related hematolymphoid can-

cer? A review of the epidemiologic literature. Clin Lymphoma 2002; 3: 36-40.
28. Mester B, Nieters A, Deeg E, *et al.* Occupation and malignant lymphoma: a population-based case-control study in Germany. Occup Environ Med 2006; 63: 17-26.
29. Seidler A, Becker N, Nieters A, *et al.* Asbestos exposure and malignant lymphoma: a multicenter case-control study in German and Italy. Int Arch Occup Environ Health 2010; 83: 563-70.
30. Pukkala E, Martinsen JI, Lynge E, *et al.* Occupation and cancer - follow up of 15 million people in five Nordic countries. Acta Oncol 2009; 48: 646-790.
31. Bianchi C, Bianchi T. Susceptibility and resistance in the genesis of asbestos-related mesothelioma. Indian J Occup Environ Med 2008; 12: 57-60.
32. Froom P, Lahat N, Kristal-Boneh E, *et al.* Circulating natural killer cells in retired asbestos cement workers. JOEM 2000; 42: 19-24.
33. Otsuki T, Maeda M, Murakami S, *et al.* Immunological effects of silica and asbestos. Cellular & Molecular Immunology 2007; 4: 261-8.
34. Nishimura Y, Miura Y, Maeda M, *et al.* Impairment in cytotoxicity and expression of NK cell-activating receptors on human NK cells following exposure to asbestos fibers. Int J Immunopathol Pharmacol 2009; 22: 579-90.

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