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ScienceDirect
Pathology – Research and Practice 205 (2009) 11–20
PATHOLOGY RESEARCH AND PRACTICE
www.elsevier.de/prp

ORIGINAL ARTICLE

Histological expression of angiogenic factors: VEGF, PDGFRα, and HIF-1α in Hodgkin lymphoma

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Received 9 March 2008; accepted 21 July 2008

Abstract

Angiogenesis is a prerequisite for solid tumor growth, but there is relatively limited data regarding Hodgkin lymphoma. The purpose of this study was to examine the immunohistochemical expression of angiogenic and proliferation markers in Hodgkin biopsies in relation to clinical parameters.

Immunostaining was performed on 65 Hodgkin biopsies with vascular endothelial growth factor (VEGF), hypoxia inducible factor-1 alpha (HIF-1α), platelet-derived growth factor receptor alpha (PDGFRα), Ki-67, and p53. Microvessel density (MVD) was determined by CD31 staining. In all cases, neoplastic cells and reactive background cells were evaluated.

The neoplastic population expressed VEGF in 48% of the cases, HIF-1α in 54% of the cases, and PDGFRα in 95% of the cases. Both Ki-67 and p53 were positive in neoplastic cells in over 60% of the cases. The MVD had a median of 2.6/0.0625 mm^2 which was not different from normal lymph nodes. VEGF in the non-neoplastic compartment showed increased staining in Ann Arbor stage I–II versus III–IV.

In conclusion, VEGF, HIF-1α, and predominantly PDGFRα are expressed in neoplastic cells in the majority of Hodgkin lymphomas. As microvessel formation is not increased in Hodgkin, additional functions of these angiogenic molecules should be investigated.

Keywords: Hodgkin; Angiogenesis; VEGF; PDGFRα; HIF-1α

Introduction

Angiogenesis is an adaptive mechanism of human tissues in response to hypoxia or increased metabolic demands. However, maladaptive angiogenesis is utilized in the pathogenesis of cancer as well as inflammatory and immune diseases [8]. Folkman [17,18] first showed

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doi:10.1016/j.prp.2008.07.007

that the establishment of new vessels is necessary for the expansion and dissemination of solid tumors, however, in hematological malignancies, there is not the same degree of evidence. Only recently, studies have been published which support a role for angiogenesis in the progression of leukemias and lymphomas [36,38,42,45,54,55].

Hodgkin lymphoma is a common lymphoma especially affecting young ages [60]. The unique histology of this cancer is due to the presence of a small percentage of malignant cells in affected tissues amongst a reactive background of non-neoplastic inflammatory, accessory cells, and a varying amount of fibrosis [60]. The role of angiogenesis in this specific type of lymphoma is still unclear. Microvessel density [13,22,28,31,35] and immunohistochemical staining of various angiogenic molecules [2,11,13,15,19,27,29,35,37,41,50] in Hodgkin lymph nodes have been reported, often with conflicting results.

The aim of this study was to examine novel angiogenic factors, such as HIF-1α and PDGFRα, in Hodgkin biopsies and their relation to the extent of angiogenesis and proliferation markers in affected lymph nodes as well as clinical parameters in the same patients.

Materials and methods

Patients

Lymph node biopsies from 65 patients with Hodgkin lymphoma were retrieved from the pathology archives of two tertiary hospitals. The study had the approval of the Ethical Committees of the institutes involved. The clinical characteristics of the patients are presented in Table 1.

Histological classification was based on the 1999 World Health Organization classification of lymphomas into nodular lymphocyte predominant Hodgkin lymphoma and classical Hodgkin lymphoma (CHL) with its 4 subdivisions: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte-rich (LR), and lymphocyte-depleted (LD) CHL. Staging was performed according to the Ann Arbor criteria [33]. Prognostic scoring was performed, where clinical data was available, according to the International Prognostic score (for advanced Hodgkin lymphoma) [24]. Other parameters taken into account included the presence of extranodular disease and the presence of B symptoms.

Standard treatment consisted of 6–8 cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) with or without involved field irradiation in 55 patients and other modalities: COPP (cyclophosphamide, vincristine, procarbazine, prednisone)/ABVD for 8 and BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) for 2 patients. After completion of therapy, patients were assessed for response.

Table 1. Patients' characteristics

	No.	%
Sex		
Male	40	62
Female	25	38
Histology		
Nodular lymphocyte predominant	1	2
Lymphocyte-rich classical HL	3	5
Nodular sclerosis	46	70
Mixed cellularity	14	21
Lymphocyte-depleted	1	2
Ann Arbor stage		
I	2	3
II	45	69
III	4	6
IV	14	22
IPS		
0	6	10
1	24	41
2	13	23
3	7	12
4	3	5
5	5	9
Extranodal extension		
Present	26	40
Absent	39	60
B symptoms		
Present	41	63
Absent	24	37
Response to chemotherapy		
Complete	43	73
Partial	13	22
Resistant	3	5
Status		
Alive	43	73
Deceased	16	27
Months of follow up		
Mean ± sd	49 ± 25	

Tissues

Immunohistochemical staining

Three micrometer sections of formalin-fixed and paraffin wax-embedded tissues were used. Sections were first dewaxed and rehydrated in alcohol. An antibody to vascular endothelial growth factor (VEGF/sc-7269, mouse monoclonal, Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA) was used at a dilution of 1:200