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SHORT COMMUNICATION

Association of haptoglobin phenotypes with the development of Kaposi's sarcoma in HIV patients

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Abstract Kaposi's sarcoma (KS) is a rare cutaneous tumor caused by human herpes virus-8 (HHV-8) infection that preferentially develops in case of severe immunosuppression, such as in HIV/AIDS disease. Haptoglobin (Hp), a polymorphic multifunctional plasma protein, exerts several immunomodulatory effects and is characterized by a genetic polymorphism leading to three major phenotypes (Hp 1-1, Hp 2-1 and Hp 2-2). This study investigated the influence of Hp genetic polymorphism on the development of KS in HIV-positive patients. 661 HIV patients were enrolled in the study with a median age of 35 years and a median follow-up time of 57 months. Hp phenotyping was performed using hemoglobin-supplemented starch gel electrophoresis. In case of low Hp concentration high pressure gel permeation chromatography (HPGPC) was used. The Hp 1-1 phenotype was associated with a significant higher risk of KS compared to the combined group of Hp 2-1 and Hp 2-2 patients ($p < 0.0005$) which remained significant after adjustment for possible confounding variables (age, gender and AIDS status) ($p < 0.001$). In contrast, the Hp 2-1 phenotype carried the lowest risk. These findings point to the involvement of Hp phenotypes in the pathogenesis of KS, which may be due to a difference in skin immunosurveillance between the Hp phenotypes.

Keywords Genetic polymorphism · Haptoglobin · HIV · Kaposi's sarcoma

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Introduction

Kaposi's sarcoma (KS) is a cutaneous viral-induced malignant tumor, which preferentially develops in immunocompromised patients. The disease presents with erythematous or violaceous macules, plaques or nodules with frequent mucocutaneous involvement. KS can extend to lymph nodes, lungs, liver, spleen and gastrointestinal tract. It was one of the earliest signs of the AIDS outbreak and has lead to major morbidity and mortality. The human herpes virus-8 (HHV-8) has been identified as the causing pathogen. HHV-8, a double-stranded DNA virus, infects primarily B lymphocytes and persists lifelong in a latent phase [16]. In case of immunosuppression, HHV-8 can be reactivated and undergo an exponential proliferation. Due to a deficient immunosurveillance, viral-induced mutations are tolerated which may lead to the development of KS [36]. In HIV patients with HHV-8 infection a 20,000- to 50,000-fold increase of KS has been reported [9]. The seroprevalence of HHV-8 infection is highly dependent on the geographic region with high percentages in areas with endemic KS such as Central Africa (±50%) and in regions

with classic KS such as the Mediterranean (±10–30%). In Western-Europe, Northern America and Asia, the seroprevalence is less than 10% [23].

Haptoglobin (Hp), an α_2-sialoglycoprotein, is a member of the family of acute phase proteins. The best known function of Hp is capturing heme-bound iron in the circulation released by hemolysis. The Hp gene is characterized by a genetic polymorphism leading to three phenotypes: Hp 1-1, Hp 2-1 and Hp 2-2. Hp phenotypes have different immunomodulating and iron-scavenging capacities which have been clinically confirmed in different pathologies including cancer and infections [14, 21, 33]. Our group previously demonstrated the association between the Hp 2-2 phenotype and a worse outcome in HIV-infected patients [5].

In this study, we investigated the role of Hp polymorphism in the development of KS in HIV-infected patients. This could provide new insights in the etiopathogenesis of KS and highlight the role of the Hp phenotype in this angioproliferative tumor with skin and visceral presentations.

Materials and methods

Patients with HIV infection were recruited from two AIDS reference centers in Belgium (Ghent University Hospital, Antwerp University Hospital) and one in Luxembourg (Centre Hospitalier de Luxembourg). Six hundred sixty one patients were enrolled [553 males and 108 females; median age of diagnosis 34 years; interquartile range (IQR) 28–42 years] in this prospective study between 1989 and 2000. The median follow-up time was 57 months (IQR 26–87 months). As the recruitment of patients for this study started in 1989 and was completed in 2000, AIDS diagnosis was based on the two main definitions produced by the Centers for Disease Control and Prevention (CDC). In the period of 1989 to 1992, AIDS was diagnosed using the 23 clinical conditions that were associated with it [25]. From 1993, the AIDS surveillance case definition was expanded to include all HIV-infected persons with $CD4^+$ T lymphocyte counts of less than 200 cells/μL or a $CD4^+$ percentage of less than 14 [26]. The diagnosis of KS was based on physician diagnosis supported by laboratory, radiologic and histopathologic results. The study was approved by the local Ethical Committee, following the ethical guidelines of the 1975 Declaration of Helsinki.

Venous blood was drawn and allowed to clot for 30 min at room temperature. After centrifugation at 1,500*g* for 10 min, the supernatant serum was collected for analysis. Hp phenotyping was performed using hemoglobin (Hb)-supplemented starch gel electrophoresis. Briefly, 11.5% hydrolyzed starch (Connaught Laboratories, Willowdale, Canada) was used to prepare a starch gel in a 0.1 mol/L Tris–citrate buffer (pH 8.86). Electrophoresis was carried out at 200 V in a 0.3 mol/L borate buffer (pH 8.4) during 1 h. The Hp–Hb complexes were visualized by staining the gel with metal-enhanced peroxidase reagents (Pierce, Rockford, IL, USA), as described previously [5]. High pressure gel permeation chromatography (HPGPG) was used in case of low plasma Hp concentration [6].

The iron status was investigated by measuring the serum ferritin concentration in the absence of an acute phase reaction [C-reactive protein (CRP) <1 mg/dL]. A latex-enhanced immunonephelometric method on a BN II analyzer (Siemens, Marburg, Germany) was used to determine serum ferritin concentration [8].

Statistical analyses were calculated with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The Hp phenotypes were compared by Mann–Whitney *U* analysis and Kruskal–Wallis test. The Chi-square test was used to investigate agreement with the Hardy–Weinberg equilibrium. Multivariate logistic regression was performed to investigate the independent effect of the Hp phenotypes on the development of KS. All values are expressed as median (IQR) and statistical significance was set at $p < 0.05$.

Results

Hundred fifteen patients were found with the Hp 1-1 phenotype, 335 subjects with the Hp 2-1 phenotype and 211 with Hp 2-2. This corresponded to allele frequencies of 0.427 for the Hp1 allele and 0.573 for the Hp2 allele. These values are similar to the allelic distributions reported from large studies in Western European populations [17]. 296 patients (44.8%) had AIDS and 51 patients (7.7%) developed KS. Seven cases of KS were diagnosed at baseline. With a total follow-up time of 3,334 years, the overall incidence was 0.018 case/year or 1 case in 55 years. Comparing the Hp phenotypes, we found 0.033 cases/year (1 case in 30 years) in the Hp 1-1 group, 0.008 cases/year (1 case in 125 years) in the Hp 2-1 group and 0.017 cases/year (1 case in 60 years) in the Hp 2-2 group.

Median age, gender distribution, frequency of AIDS-positive patients and median follow-up time were similar between the different Hp phenotypes (Table 1). As reported earlier [5], the mortality in the Hp 2-2 group was significantly higher than in the Hp 1-1 and Hp 2-1 group. The occurrence of KS was markedly different between the Hp types. In the Hp 1-1 phenotype group, 19 patients (16.5%) developed KS; in the Hp 2-1 group, 15 patients (4.5%) and in the Hp 2-2 group, 17 patients (8.1%). Multivariate logistic regression analysis with adjustment for age, gender and AIDS status showed an increased development of KS in patients with the Hp 1-1 phenotype ($p < 0.0005$) (Table 2). In patients without AIDS, the influence of the

Table 1 Characteristics of the study population according to the Hp phenotype

	Hp 1-1 phenotype ($n = 115$)	Hp 2-1 phenotype ($n = 335$)	Hp 2-2 phenotype ($n = 211$)	p value
Age (years)	34 (29–41)	34 (27–43)	36 (28–43)	n.s.
Gender (males %)	87.0 ($n = 100$)	83.0 ($n = 278$)	82.0 ($n = 173$)	n.s.
Aids (%)	46.1 ($n = 53$)	42.7 ($n = 143$)	46.9 ($n = 99$)	n.s.
Mortality (%)	21.7 ($n = 25$)	23.3 ($n = 78$)	32.2 ($n = 68$)	0.025
Median follow-up time (months)	50 (25–90)	63 (27–88)	50 (25–82)	n.s.
Kaposi's sarcoma (%)	16.5 ($n = 19$)	4.5 ($n = 15$)	8.1% ($n = 17$)	<0.001

n.s. not significant

Table 2 Logistic regression model of KS development according to Hp phenotypes

	β	Wald χ^2	Odds ratio (95% CI)	p value
Model 1 (multivariate)				
Hp 1-1 vs. Hp 2-1 and Hp 2-2				
Hp 1-1 type	1.199	13.820	3.31 (1.76–6.26)	<0.0005
Age	0.020	2.825	1.02 (1.00–1.04)	n.s.
Gender	0.493	0.816	1.64 (0.56–4.76)	n.s.
AIDS	1.255	13.488	3.51 (1.80–6.85)	<0.0005
Model 1 (univariate)				
Hp 1-1 vs. Hp 2-1 and Hp 2-2				
Hp 1-1 type	1.155	0.310	3.17 (1.73–5.83)	<0.0005
Age	0.025	0.011	1.03 (1.01–1.05)	<0.05
Gender	0.893	0.532	2.44 (0.86–6.93)	n.s.
AIDS	1.383	0.332	3.99 (2.08–7.64)	<0.0001
Model 2 (multivariate)				
Hp 2-1 vs. Hp 1-1 and Hp 2-2				
Hp 2-1 type	0.942	8.491	0.39 (0.21–0.74)	<0.005
Age	0.018	2.293	1.02 (1.00–1.04)	n.s.
Gender	0.545	0.999	1.72 (0.59–5.02)	n.s.
AIDS	1.226	12.986	3.41 (1.75–6.64)	<0.0005
Model 2 (univariate)				
Hp 2-1 vs. Hp 1-1 and Hp 2-2				
Hp 2-1 type	−0.971	0.318	0.38 (0.20–0.71)	<0.005
Age	0.025	0.011	1.03 (1.01–1.05)	<0.05
Gender	0.893	0.532	2.44 (0.86–6.93)	n.s.
AIDS	1.383	0.332	3.99 (2.08–7.64)	<0.0001

Hp 1-1 phenotype was more pronounced ($p < 0.005$) compared to patients with AIDS, where only borderline significance was reached ($p = 0.059$) (Fig. 1a–c). Bias due to an increased frequency of mortality in the Hp 2-2 group is unlikely as the median follow-up time was very similar in the Hp 1-1 group compared to the Hp 2-2 group (Table 1). The Hp 2-1 phenotype was associated with the lowest risk of KS development ($p < 0.005$) (Table 2). Ferritin values, measured in 128 patients, were lowest in patients with Hp 1-1 phenotype [111 μg/L (49–194 μg/L)], followed by Hp 2-1 [131 μg/L (69–211 μg/L)] and Hp 2-2 patients [195 μg/L (107–401 μg/L)].

Discussion

As a consequence of the progress in highly active antiretroviral treatment (HAART) the incidence of KS has decreased dramatically. This was confirmed in our study, since no new cases were diagnosed in the period 1997–2000. Nonetheless, KS may also develop in patients with CD4 counts exceeding 200 μL^{-1} [22]. Current treatments for KS (including HAART and chemotherapy) are insufficient to induce complete regression in up to half of the patients [24]. As HIV patients have increasing survival expectations, the future evolution of the incidence of KS on the aging HIV-population is unknown [38]. This implicates that studies of biomarkers identifying a subset of patients at increased risk for KS remain useful.

Our study points to an increased susceptibility of Hp 1-1 patients for the development of KS. A less effective immune response associated with the Hp 1-1 phenotype may partially explain this finding. Hp downregulates T cell proliferation and induces a shift to a Th2 balance which may favor the persistence of viruses [27]. Hp 1-1 complexes phagocytosed by macrophages result in higher Interleukin (IL)-6 and IL-10 levels compared to Hp 2-2 complexes. Interestingly, HHV-8 infection of dendritic cells also induces a Th2 response [13]. IL-6 is overexpressed in patients with KS and in a subset of HHV8+/HIV+ patients, viral-IL-6 can lead to a systemic inflammatory syndrome even in absence of Castleman disease [37]. In transplant patients, a polymorphism in the promoter of the IL-6 gene was associated with an increased risk of KS [11]. IL-6 may play a role in cellular proliferation of HHV-8 infected cells and inhibit apoptosis favoring tumoral development [42, 44].

Hp is mainly produced by the liver, although a small fraction is synthesized by keratinocytes in the skin.

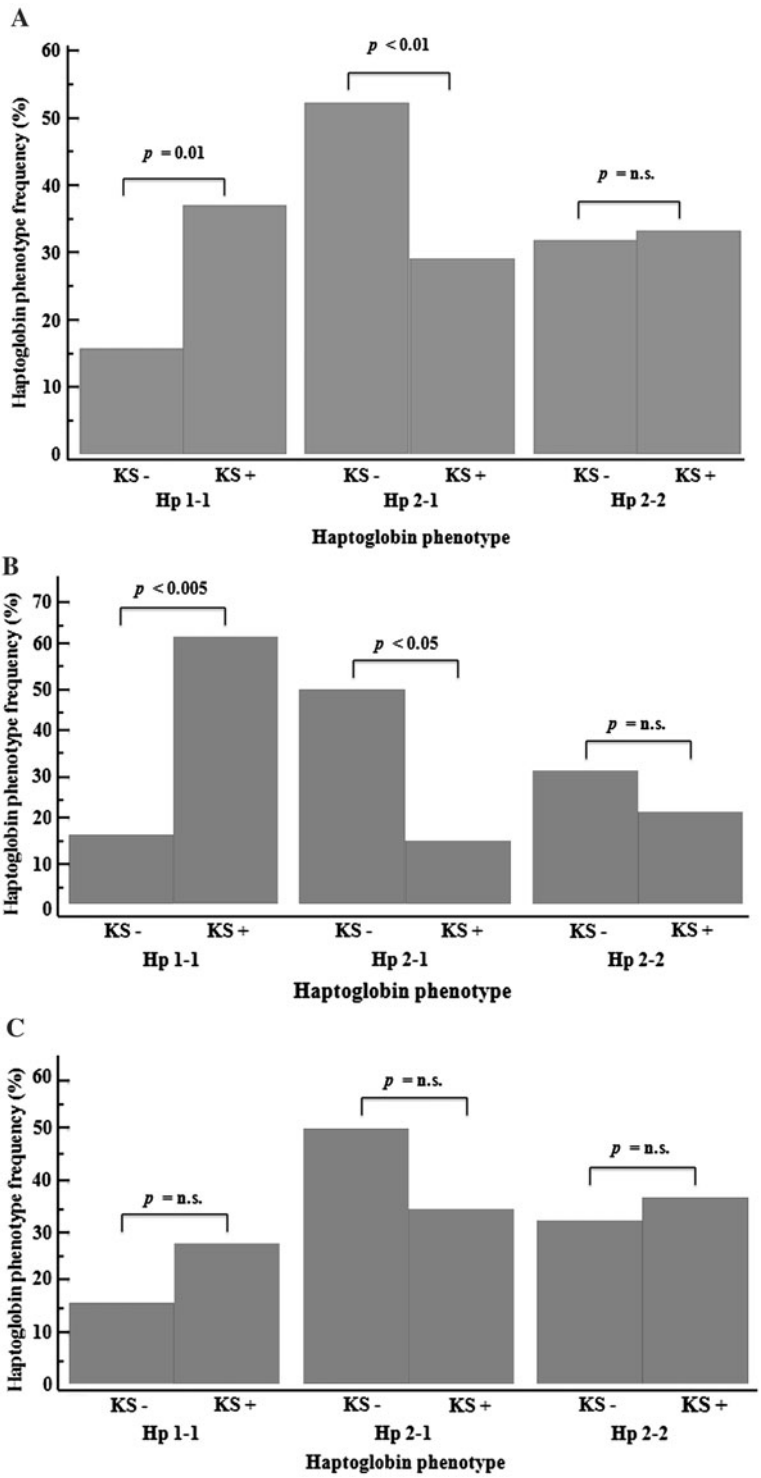

Fig. 1 **a** Hp phenotype distribution in patients (combined group of subjects with HIV or AIDS) with (*right*) and without (*left*) Kaposi's sarcoma (KS). A significant difference in the haptoglobin (Hp) phenotype frequency was found in the Hp 1-1 ($p = 0.01$) and in the Hp 2-1 group ($p < 0.01$). **b** Hp phenotype distribution in HIV patients with (*right*) and without (*left*) Kaposi's sarcoma (KS). A significant difference in the haptoglobin (Hp) phenotype frequency was found in the Hp 1-1 ($p < 0.005$) and in the Hp 2-1 group ($p < 0.05$). **c** Hp phenotype distribution in AIDS patients with (*right*) and without (*left*) Kaposi's sarcoma (KS). No significant difference in the haptoglobin (Hp) phenotype frequency was found. n.s. = not significant

Moreover, Hp is found in Langerhans cells (LCs) which is probably due to transfer of Hp from surrounding keratinocytes. Hp 1-1 is characterized by the highest concentration of Hp, which may result in a more impaired activity of LCs compared to the other phenotypes as Hp inhibits the functional maturation of LCs [43]. A decreased function of LCs is considered as a primary event in the development of KS. Human leukocyte antigen (HLA)-DR + LCs are found in decreased numbers in KS lesions [1, 39]. Remarkably, the Hp 2-1 phenotype was a stronger preventive factor to KS development compared to the Hp 2-2 phenotype. This may be due to the higher serum iron concentration, higher transferrin saturation and higher ferritin values reported in Hp 2-2 males, but not in females, than in Hp 1-1 and Hp

2-1 subjects [7]. Multiple studies have described the role of cellular iron in the carcinogenic pathways [15, 20, 29, 34, 40]. However, the pathogenic role of iron in cancer development and/or progression is not fully understood [32]. In comparison with a healthy population, ferritin concentrations are higher in HIV-infected patients [5]. More specifically in cases of KS, the addition of iron salts to KS-derived cells can stimulate their growth [30]. In human dermal microvascular endothelial cells, iron can induce antiapoptosis, which may alter the homeostasis of microvessels and promote neo-angiogenesis [31]. At the early stages of KS development, red blood cell extravasation and the presence of siderophages are encountered, providing a possible continuous source of iron for endothelial and KS cells. Moreover, on histopathological examination, ferritin granules and hemosiderin-loaded macrophages are regarded as the hallmark of KS [32]. Hp 2-2 subjects accumulate more iron and oxidize more vitamin C, suggesting that less efficient protection against hemoglobin/iron-driven oxidative stress may be a direct mechanism for stimulating viral replication [5].

Hp is a multifunctional protein exerting both immunomodulating and iron-scavenging properties. On the one hand, Hp 1-1 has the least inflammatory properties, but on the other hand, the Hp 2-2 phenotype is associated with higher iron levels. Moreover, the three phenotypes have a markedly different molecular structure. As the development of Kaposi sarcoma has also a multifactorial pathophysiology, this may explain why the Hp phenotypes show no gradual change. Previous research has shown that the Hp 2-1 phenotype is not always associated with an intermediate risk, which is nicely discussed in a letter regarding the finding of an increased risk of the Hp 2-1 phenotype for rapid growth of abdominal aortic aneurysms [41]. A similar finding was observed in patients with Legionnaires' disease. Using a multivariate analysis, Hp 2-1 was an independent risk factor for the more severe cases. This association was not influenced by age and could not be explained by differences in serum ferritin, iron and transferrin saturation [19]. The phenomenon of an enhanced or decreased risk for heterozygous individuals has been termed molecular heterosis [3].

Recently, several studies stressed the protective effect of functional promoter single nucleotide polymorphisms (SNPs) of the Hp gene to the susceptibility to infections. The base substitutions -61A-C (rs5471) and -101C-G (rs5470) within the 5′ flanking region of the Hp gene are, respectively, associated with ahaptoglobinaemia and hypohaptoglobinaemia [35]. In two independent cohort studies of Gambian children, Hp gene promoter polymorphisms affected susceptibility to malaria (*Plasmodium falciparum*) [4] and trachoma (*Chlamydia trachomatis*) [28]. As the -61A-C and the -101C-G Hp promoter SNPs are highly linked with the Hp2 and Hp1S allele, respectively, those SNPs may also be involved in the development of Kaposi's sarcoma in HIV patients. Further investigations should focus on the possible associations between Hp promoter SNPs and HHV-8 infection. Besides the Hp phenotypes, polymorphisms in other genes involved in the host immune response have previously been investigated. In HIV patients, the VF genotype of FcγRIIIA was associated with KS risk, while the FF genotype was characterized as a protective factor [18]. HLA-DRB1 alleles with phenylalanine at position 13 instead of glycine had an increased risk for KS [10]. Studies of classic KS identified diplotypes of the interleukin-8 receptor-β (IL8Rβ, 1235T/1010G) and IL-13 (promoter region variant 98A) as predisposing factors. Furthermore, polymorphisms in HLA have been linked to KS and HHV-8 shedding [2, 12]. Our findings pointing to an association of the Hp 1-1 phenotype with an increased risk for KS add additional evidence to the role of genes involved in the immune response in the pathogenesis of KS.

In conclusion, we found a significant difference in development of KS in HIV patients, according to their Hp phenotypes. If confirmed, HIV patients with the Hp 1-1 phenotype are at increased risk for KS development which may be due to a decreased skin immunosurveillance associated with this phenotype.

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