Reviews in Clinical Medicine

Correlation between Human Herpes virus 8 (HHV-8) and Plasma Cell Myeloma: a Systematic Review

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ARTICLE INFO	ABSTRACT
Article type Systematic review **Article history** Received: 27 Jun 2018 Revised: 7 Aug 2018 Accepted: 10 Sep 2018 **Keywords** Etiology Human herpes virus 8 Multiple Myeloma	**Introduction:** Plasma cell myeloma is the distortion of differentiated B lymphocytes which is associated with uncontrolled proliferation of plasma cells in bone marrow. Some studies propound a role for HHV-8 virus in pathogenesis of plasma cell myeloma. Yet the findings are inconsistent. In this article we reviewed the literatures to determine the HHV-8 virus role in plasma cell myeloma pathogenesis. **Methods:** In this systematic review, scientific databanks including PubMed, Scopus, Embase, ISI, and Google scholar were searched. The search was based on the subsequent keywords and medical terms in title; different combinations of keywords were used, they were compatible with MeSH terms. **Result:** Four articles declared that there is no link between the HHV-8 and the pathogenesis of plasma cell myeloma; while five reported a connection between the virus and myeloma, arguing that virus infection will lead to disease progression. **Conclusion:** There are differences between the results of the studies. It is required to do further researches about the association of HHV-8 and plasma cell myeloma.

Introduction

Plasma cell myeloma is the distortion of differentiated B lymphocytes which is associated with uncontrolled proliferation of plasma cells in bone marrow. Almost 3% of plasma cell myeloma and MGUS (Monoclonal Gammopathy of Undetermined Significance) patients have more than 10% plasma cells in bone marrow; it can reach to 85% in advanced cases (1). Abnormal production of para-proteins which are found in serum and urine is responsible for lytic bone lesions in skull, pelvis and thighs (2).

Plasma cell myeloma outbreak usually happens in the seventh decade of life and it is more prevalent in males. Although the primary cause of plasma cell myeloma is unknown, many factors such as age, obesity, male gender, exposure to ionizing radiation, African race and history of MGUS can increase the risk of plasma cell myeloma (3,4). Infection is the primary cause of death in about 45% of multiple myeloma (MM) patients (5). Some studies have found viruses spread in plasma cell myeloma.

In 1994 Chang and colleagues discovered a type of herpes virus in Kaposi's sarcoma cancer cells in patients infected with HIV; it was named Kaposi's sarcoma associated herpes virus, today it is called HHV-8 (human herpes virus type 8) (6).

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HHV-8 genome is a 170 kb linear double strand DNA. Assembled sequences of virus genome are able to replicate in the host cell and disrupt cytokine production and regulation. Some clinical trials studied the role of some proteins such as Analog viral interleukin-6 (vIL-6), complement-binding proteins, three separate macrophage inflammatory protein (MIP) and human IL-8 receptor in pathogenesis of viral analog and malignant transformation of human cells (7-10).

Oncogenic alteration of KSHV genome and related immunological disorders depends on some cofactors such as viral oncogenes, cytokine regulation and immune system status (11). HHV-8 virus interferes with the normal function of the immune system and inhibits the antiviral activity of the immune cells. Virus infected B lymphocytes cannot activate other lymphocytes; In addition infected T lymphocytes are unable to tolerate cytotoxic effects of the virus which lead to apoptosis. The virus is able to live and proliferate in human endothelial and epithelial cells (12,13).

The incubation period is unknown and little information is available from primary infection with HHV-8 virus. Disorders associated with HHV-8 infection are Kaposi's sarcoma, Castleman disease, plasma cell myeloma, angiosarcoma, lymphoma and body cavity lymphoma. In all the above, it seems that illness will initiate or aggravate after the primary infection with virus is established (14).

In several studies HHV-8 has been isolated from bone marrow stromal dendritic cells in patients with plasma cell myeloma. Since the myeloma cell growth factor is IL-6, viral IL-6 (vIL-6) is a major agent in plasma cell myeloma pathogenesis. But still complete and accurate relationship between HHV-8 and plasma cell myeloma disease has not been determined; the theory is still under investigation (15-18). The purpose of this study was to review and examine the relationship between the HHV-8 virus and plasma cell myeloma, in order to clarify the new aspects of diagnosis and treatment for cited malignancy.

Methods
Search strategy and article selection
This systematic review was performed in June 2018; scientific databanks including PubMed, Scopus and Embase, ISI, Cochrane library and google scholar were searched; the search was based on the following keywords or medical subject terms in titles. Different combinations of keywords were applied for searching including: "HHV-8" and "Multiple myeloma" or "KSHV" and Multiple myeloma, "Human herpes virus 8" or "HHV-8" and "Multiple myeloma", "Kaposi's sarcoma-associated herpes

virus" or "KSHV" and "Multiple myeloma". The keywords were compatible with MeSH terms.

The review article followed the Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) plans. The PRISMA Diagram was adopted to summarize the results of the involved studies (Figure 1). The last search was carried out in November 2016.
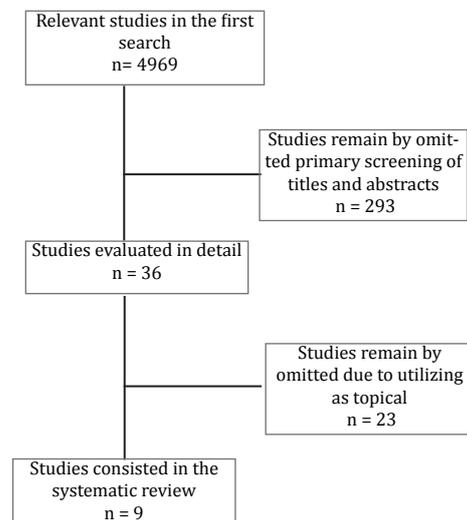

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses.

This study was limited to English language papers. The references of cohort studies were searched. In order to find studies which could not be found via computerized search, references of all relevant studies were reviewed. The titles and abstracts of searched papers were studied by one author (Z. Rezaei). Full texts were screened by another author (Dr. MH. Sadeghian). Relevant information was extracted from each article independently by two authors (F. Shams and S. Shakeri). After reaching sufficient agreement, the information was extracted by one person and checked by the second one.

In the present study, the inclusion principles were as following: 1) Published English clinical trials before November 2016; 2) Survival information based on HHV-8 infection and MM; 3) Articles about the HHV-8 prevalence in MM patients; 4) Studies that included information about MM prognosis in association with HHV-8 virus.

All papers were evaluated based on the inclusion criteria and were compared according to their titles and abstracts. Then, full texts of the articles, which encountered the inclusion criteria, were obtained.

The exclusion criteria were as monitors: 1) Articles counting fewer than 10 patients; 2) Editorial articles, case reports and review; 3) Articles in a language other than English; 4) Conferences and

seminars related to the subject were excluded. We use one short communication article, because it was completely related to the topic of the study; 5) samples obtained from cell or tissue cultures; 6) Animal models of plasma cell myeloma.

Quality evaluation

The quality of the enrolled articles was evaluated by two authors according to the Cochrane risk of bias tool. A quality review involved random sequence generation (selective bias); allocation concealment (selective bias); optional reporting (reporting bias); blinding of contributors and staff (performance bias); blinding of results evaluation (detection bias); defective outcome data (attrition bias); and other kinds of bias (19). Based on the quality valuation principles, each article was distributed into three different classes. If all standards were met, we ranked it as class A (low risk of bias). When more than one standard was not reached or was unclear it was graded as class B (unclear risk of bias). The valuation also suggested class C, if none of the standards were reached (high risk of bias). The discrepancies between reviewers resolved via discussion.

The collected documents involved information based on PRISMA guidelines. Data were composed of authors' information, year of publication, region of study, patient clinical and laboratory information including: age range, presence of antibodies against virus, history of HHV infection. All the extracted information and results were included in the study; the authors did not have any interventions in this regard.

Results

In the initial search, 4969 articles were obtained, of which 4700 were in the Google Scholar database, 142 articles in the PubMed, 51 in the Scopus, 49 in the Embase, 26 articles in the Web of Science database and 1 in the Cochrane library. By studying the titles and abstracts, 293 related articles were found. 36 articles were obtained by removal of duplicate articles and conferences and non-English articles. By reviewing the full text of 36 selected papers, 23 articles were examined and 9 of them were compatible with inclusion criteria. As it was mentioned before, one short communication which was completely related to the topic was selected.

Data was extracted from nine selected articles. The properties of the studies assessing HHV-8 prevalence in Plasma cell myeloma patients, are summarized in Table 1. The patient population of the selected articles was from various countries and groups. All papers contained information about the question under study. All the patients with plasma cell myeloma, contributing in these studies, aged within the range of 38 to 85 years.

Immunohistochemistry method was used by 2 studies which did not find virus significantly (20,21). The results indicated no relationship between HHV-8 virus and Plasma cell myeloma.

Nested PCR was used by 6 studies (20,22-26); 4 out of 6 found HHV-8 virus and reported an association between the virus presence and the disease (22,23,25,26). Sequencing method was performed for positive samples by 3 researches (23,25,26). One study reported HHV-8 strain pattern consistent with C3 subtype in analysis of ORF26 (25). Other studies applied SSCP assay which revealed 6 distinguishable patterns with different point mutations among the patients (23).

Of the articles reviewed, four articles declared that there is no link between the HHV-8 and plasma cell myeloma pathogenesis (20,21,24,27). Completely reverse results have been obtained by 5 groups of researchers; they stated that HHV-8 infection may lead to disease progression in some cases (22,23,25,26,28). It seems that differences in the applied methods have led to differences in reported results.

Discussion

The etiology of MM is generally unidentified; it is a malignant proliferation of plasma cells which produce abnormal quantities of monoclonal immunoglobulin or its fragments (29). Some studies have proposed a pivotal role of viruses in the expansion of MM. Yee et al. (30) and Dokekias et al. (31) found a possible relationship between HIV and MM.

Csire et al. (22) declared that HHV-8 is one of the effective factors in the pathogenesis of MM. They evaluated the presence of EBV, cytomegalovirus (CMV), HHV6 and HHV-8 in MM cases using serologic methods and nucleic acid amplification techniques (NAT). They identified cited viruses in 36, 8, 13 and 29 of 69 patients with MM, respectively; and also 9, 1, 4 and 6 of 16 MGUS patients, respectively.

Gao and colleagues examined serum samples of plasma cell myeloma patients, including Different race and Hispanic. According to their report 81% of MM patients were KSHV-seropositive by the ORF65 serologic assay. 52% were seropositive by the LNA immunoblot assay (odds ratio, 3.08; 95% confidence interval, 0.85-11.43). Of 14 LNA-seropositive patients, 13 individuals were also ORF65 seropositive. They also tested bone marrow samples of a separate cohort of patients with plasma cell myeloma for the presence of anti-KSHV antibodies; half of these samples were seropositive, tested by ORF65 immunoblotting assay.

Table 1. Data extracted from studied articles a bout the correlation between HHV8- and plasma cell myeloma.

First authors country Year Referencs	plasma cell myeloma patients			Control			Methods	p-value	Gender	age	Patient stage	Patient samples
	All (n)	positive n	positive %	All (n)	positive n	positive %						
Sonja _J Olsen USA 1998 (16)	25	5	20	70	8	11	serology	0.0005	NR	NR	NR	Formalin _ fixed,paraffin_embeded bone marrow biopsies
	25	3	12	70	5	7	Western blot	NR				
	16	0	0	4	0	0	IHC	NR				
Scotta A.stone USA 2000 (17)	11	8	73	17	2	12	Serology(light chain)	0.045	NR	NR	NR	Serum or plasma
	38	12	32	17	2	12	Serology(IgG,IgA)	0.033				
Shou.Jiang Gao Texas 1998 (19)	27	22	81	27	6	22	serologic	NR	18 Male 9Female	(27_81) Mean69:	Stage 1: 1 Stage 3: 26	Plasma and serum
	27	14	52	27	7	26	immuno-blot	NR				
Hiu_chi Hsu Taiwan 2001 (20)	49	22	44.9	8	0	0	Dot blot analysis	NR	44 Male 5Female	(36_79) Mean : 63	Stage 1: 4 Stage 2: 4 Stage 3: 41	Bone marrow Biopsy
	49	20	40.8	8	0	0	PCR	NR				
Mohammad hadi Sadeghian Iran 2013 (21)	30	0	0	30	1	3.33	PCR	0.999	14 Male 16 Female	(40_80)	All patient was symptomatic stage	FFPE (Formalin _ fixed,paraffin_embeded bone marrow biopsies)
M.Beksac USA , Turkey 2001 (22)	21	17	80.95	11	0	0	PCR	NR	NR	NR	NR	Bone Marrow Biopsy
Mohammad hadi Sadeghian Iran 2008 (23)	30	4	13.3	30	0	0	IHC	0.11	22 Male 18Female	(83_38)	NR	FFPE (Formalin _ fixed, paraffin_embeded bone marrow biopsies)
Said I.Ismail Jordan 2010 (24)	17	7	41	18	0	0	PCR	0.003	13 Male 4 Female	NR	Stage 1A: 6 Stage 2A: 2 Stage 3A: 3 Non stage6	Bone Marrow Aspirates
Marta Csire Hungary 2006 (18)	69	29	42	44	1	1	PCR	P<0.000	NR	NR	Stage 2: 21 Stage 3: 48	Bone marrow aspirates And blood samples with EDTA
	52	4	8	26	0	0	serologic	NS				

NR= Not Report, NS= Not Significant

Finally, they concluded that presence of anti-KSHV antibody is not correlated with ethnicity, age, sex, duration of disease after diagnosis, levels of myeloma monoclonal protein or b2-microglobulin at the time of serum sampling. They confirmed increased prevalence of KSHV infection in patients with plasma cell myeloma (28).

Hsu and colleagues studied bone marrow biopsy samples. They did not detect KS330233 (ORF 26 Antigen) in the initial PCR products of MM patients. However, in 186–base-pairs of N-PCR products, KSHV-specific genetic amplifiers were detected in 40.8% of MM patients. The specificity of N-PCR products were confirmed by dot blot analysis; it showed that KSHV DNA sequence was found in 44.9% of studied patients, including all N-PCR positive and 50.2% of N-PCR negative ones. Finally, they supported the idea that HHV-8

is detectable in myeloma patients (23).

Sadeghian et al. studied bone marrows of 30 myeloma patients in symptomatic phase; they reported 2 positive cases of HHV-8 in men and 2 in women (21). On the other hand they did not find any viral HHV-8 genomes in another study which was done on plasma cell myeloma patients (24). Their results rejected the link between HHV-8 and myeloma; it seems that disagreement is due to the measurement methods. Contrariwise to Sadeghian's study, Said et al. in evaluation of bone marrow samples of 17 Jordanian plasma cell myeloma patients, has rejected any connections between HHV-8 and plasma cell myeloma (26).

Beksac an American researcher studied 24 individuals with monoclonal gammopathy including 21 patients with MM and 2 patients with MGUS and 1 with plasmacytoma. Specific amplified products for KS330 233(ORF 26) primers were observed in 17 of 21 (80.95%) MM patients. Viral genome was detected in 13 of the 15 newly diagnosed MM by DNA-PCR method.

29 monoclonal gammopathy samples including 14 (48.27%) individuals with plasma cell diseases, and control group were analyzed in Turkey, independently. The obtained results were similar with the US Laboratory, completely. Analysis of ORF26 sequence demonstrated HHV-8 strain pattern consistency with a C3 subtype. Accordingly, they supported the idea of HHV-8 presence and myeloma. This is noteworthy that these two studies are conducted in two separate laboratories in the areas with different races (25).

Bellos and colleagues performed PCR technique to detect the KSHV in 35 samples of leukopheresis (LP) products of myeloma patients. Of the 35 patients with plasma cell myeloma 34 patients were in progressive phase of the disease (32). Analysis of LP aliquots of 35 patients with MM did not show any KSHV-specific amplification products after first-round of amplification; although the positive control was clearly visible. Second-round of amplification was done to confirm the negative PCR of LP aliquots of 27 patients after gel electrophoresis. Interestingly, in 8 patients the second round of PCR bands with the same size of the positive individuals appeared. However, none of the bands hybridized with the marked KSHV probe; none of the sequences disclosed any similarities to the KS330 233 sequence of the virus genome.

Conclusion

According to the survey conducted studies, further investigations in larger group of patients with monoclonal disorders are needed. It is recommended to use more advanced diagnostic methods in order to get a definite answer to the question whether or not the HHV-8 is associated with plasma cell myeloma disease.

Acknowledgement

Conflict of Interest
The authors declare no conflict of interest.

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