High prevalence of originally-mutated KSHV contributes to the high incidence of non-AIDS associated Kaposi's sarcoma in isolated Japanese islands

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Introduction

- Classic Kaposi's sarcoma (KS) usually occurs in elderly men and those prevalence is high in particular regions and ethnic groups.
- In Japan, KS is mostly occurred as a symptom of AIDS, and non-AIDS associated KS (non-AIDS KS) is very rare.
- But Okinawa, the southernmost prefecture of Japan, is exceptionally endemic area of non-AIDS KS.
- We aimed to elucidate the exact incidence and cause of this high prevalence in the region.

1. Kaposi's sarcoma (KS) in Japan and Okinawa

- KS patient of 31 years (1984-2014) were collected and reviewed.

Kaposi's sarcoma (1984-2014)	Okinawa prefecture (population: 1.29×10 ⁶)		Mainland Japan (population: 123×10 ⁶)
Clinical type	AIDS related	non-AIDS related	non-AIDS related
Number of Cases	13 cases	60 cases (Classic 38 cases latrogenic 22 cases)	79 cases (Classic 58 cases latrogenic 21 cases)

2. Origin of non-AIDS KS of Okinawa

- Half of the non-AIDS KS patients of Okinawa were from Miyako Islands, though population of Miyako Islands is less than 5% of Okinawa Prefecture.

(No. of non-AIDS Kaposi's sarcoma patients/population)

3. Comparison of yearly non-AIDS KS incidence rate (≥50years old)

		Mainland Japan	Okinawa (excluding Miyako)	Miyako Islands
Male	Population(≥50y)	2.0×10 ⁷	1.7×10 ⁵	9.7×10 ³
	No. of cases	51	17	25
	Incidence rate (/100000/year)	0.0082	0.33	8.3
Female	Population(≥50y)	2.4×10 ⁷	2.0×10 ⁵	1.1×10 ⁴
	No. of cases	23	13	5
	Incidence rate (/100000/year)	0.0031	0.15	1.4
Male/Female ratio		2.6	2.2	5.9

- The incidence rates of Miyako Islands was comparable to those in the Sardinia Islands*: the most famous endemic area of KS. (*Vitale F, et al. Int J Cancer 91, 2001)

Q: Why dose people in Okinawa, especially of Miyako Islands, tend to develop Kaposi's sarcoma?

1. High KSHV seroprevalence? 2. Distinctive KSHV? 3. Genetic variance?

1. High KSHV seroprevalence?

- We have surveyed HHV8 seroprevalence in Miyako Islands with ELISA*.

KSHV seroprevalence in Miyako Islands			
Age	Male	Female	Total (n=1132)
10-29	7.7%	5.3%	5.9%
30-49	1.8%	4.7%	3.7%
50-69	12.8%	15.2%	13.9%
70-	23.0%	19.7%	21.6%
Total	16.6%	14.1%	15.4%

- KSHV seroprevalence in Miyako Islands (15.4%) was 11 times higher than those of Okinawa Islands* (1.4%) and Japan** (1.4%). (*Katano H, et al. J of Virology 74, 2000, **Sato M, et al. Jpn J Infect Dis 54, 2001)
- Considering the different seroprevalence, we next calculated the non-AIDS KS incidence rate among KSHV carrier.

Summary

- Okinawa prefecture, especially Miyako Islands, is one of the worldwide endemic area of non-AIDS related Kaposi's sarcoma.
- KSHV seroprevalence of people in Miyako Islands was 15.4%, that was 11 times higher than those of Okinawa Islands and Japan. But this gap alone was not enough to explain high frequency of non-AIDS Kaposi's sarcoma in Miyako and Okinawa.
- KSHV genome of Miyako Islands formed a phylogenetically distinct branch from those of previously sequenced KSHV and shared specific mutations in 9 proteins.
- Whole-exome sequencing of the 4 male Miyako Islanders could not revealed the possible Kaposi's sarcoma susceptibility genes so far.
- We believe that the combination of characteristic KSHV strains and ethnic background bring the frequent Kaposi's sarcoma development in Miyako and Okinawa.

Yearly incidence rate of non-AIDS Kaposi's sarcoma among KSHV carrier (≥50years old)

		Mainland Japan	Okinawa (excluding Miyako)	Miyako Islands
Male	Incidence rate	0.0082	0.24	8.3
	HHV8 infection rate	2.4	1.0	18
	Incidence rate among carrier (%)	0.00034	0.032	0.045
Female	Incidence rate	0.0031	0.15	1.4
	HHV8 infection rate	2.4	2.4	18
	Incidence rate among carrier (%)	0.00013	0.089	0.008
Male / Female ratio		2.7	3.7	5.6

- Different seroprevalence was not enough to explain different incidence rate between Mainland Japan and Okinawa area (more than ×60).

2. Distinctive KSHV around Okinawa?

- Then we compared the KSHV whole viral genome from non-AIDS KS tissue of Miyako Islands (3cases) and Mainland Japan (1case) by NGS.

- KSHV of Miyako shared common mutations in following 9 viral proteins, compared to KSHV of mainland Japan: K1, ORF24, ORF26, ORF30, ORF42, ORF70, ORF72, ORF73, vIRF-2

3. Genetic variance?

- Okinawa has experienced unique genetic and cultural development.
- To find out possible KS susceptibility genes, we performed Whole-Exome sequence of 4 male non-AIDS KS patients of Miyako origin.

We were unable to identify a shared pathogenic mutations via exome analysis.

4. Conclusion and future prospect:

- Though the exact reason, other than high KSHV seroprevalence in Miyako Islands, remains to be excluded, we believe that characteristic KSHV and ethnic background may influence KS development in Miyako Islands and Okinawa area.