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Case Report

Endogenous Reactivation rather than Primary Infection of Sexually Transmitted Viruses in the Community during the Early Phase of the COVID-19 Pandemic in Hong Kong

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Abstract

Aim: We aim to report a retrospective epidemiological study on patients with sexually transmitted infections during the early phase in the COVID-19 pandemic.

Methods: Our settings is a primary care genito-urinary medicine clinic with two sessions per week, attached to a major university teaching hospital. We searched and hand-reviewed the medical records of all patients having consulted us during a Pandemic Period of 90 days (1 February to 30 April 2020). We then reviewed records of all patients having consulted us in two Control Periods each of 90 days before the pandemic. We analysed the records with final diagnoses most likely being sexually-transmitted only.

Results: During the Pandemic Period, 61 episodes of sexually transmitted infections were diagnosed, significantly less than such in the Control Periods (360 episodes in 180 days; RR: 0.34, 95% CI: 0.25-0.45). The commonest pathogens were

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1. Herpes simplex-2 or -1 (recurrent episodes)
2. Human papillomavirus (recurrent episodes)

During the Pandemic Period, only one out of 24 patients with herpes simplex-2 or -1 infection was a first attack. This rate was significantly lower than such in Control Period 1 (RR: 0.12, 95% CI: 0.02-0.81), Control Period 2 (RR: 0.13, 95% CI: 0.02-0.93), and both Control Periods combined (RR: 0.12, 95% CI: 0.02-0.86).

For human papillomavirus infection, during the Pandemic Period, only one out of 20 patients presented with the first attack. This rate was also significantly lower than such in Control Period 1 (RR: 0.12, 95% CI: 0.02-0.86), Control Period 2 (RR: 0.13, 95% CI: 0.02-0.87), and both Control Periods combined (RR: 0.12, 95% CI: 0.02-0.85).

Conclusions: Endogenous reactivations of sexually-transmitted herpes simplex viruses and human papillomaviruses were significantly more frequent than primary infections during the early phase of the COVID-19 pandemic. This may be associated with less sexual exposures and psychosocial stressors compromising cell-mediated immunity.

Keywords

Chlamydia Trachomatis; Endogenous Reactivation; Genito-Urinary Medicine; Gum Clinic; Herpes Simplex Virus; Human Papillomavirus

Introduction

During the early phase of the COVID-19 pandemic, we noted specific and unanticipated changes in the incidence of citizens in the community consulting us for suspected or confirmed Sexually Transmitted Infections (STI). We report here these changes and postulate the underlying mechanisms.

Materials and Methods

Our aim is to report a retrospective epidemiological study on patients with STI in the community during three months in the early phase of the COVID-19 pandemic.

Our settings is a Genito-Urinary Medicine (GUM, synonymous with venereology) clinic two sessions per week in a primary care setting, attached to a major university teaching hospital. It is served by a Specialist in Family Medicine with training and qualifications in GUM. Comprehensive services for the prevention and management of STI, including contact tracing

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and patient education, are offered. Skin problems in the genital regions for both sexes are diagnosed and managed. Most patients make appointments beforehand. However, walk-in consultations are also available. Most patients are not referred by other medical practitioners.

We have adequate laboratory support including DNA sequence-based investigations. However, the costs of investigations are borne by the patients. As reported previously, we apply dermoscopy to confirm clinical diagnoses when necessary [1]. Patients with hepatitis B or C virus infections are managed in hepatology clinics and in the hospitals. The GUM clinic only offers screening for the serologies. Regular cervical smear screening is also not a conventional service offered in our clinic.

Hong Kong saw her first patient with confirmed COVID-19 on 22 January 2020 [2]. Our clinical services were largely unaffected, with isolation and sterilisation measures strictly adhered to in order to protect the staff and the patients. A change in the number of consultations and the incidences of several STI were noted by us shortly.

In June 2020, we searched our computerised registers and hand-reviewed the medical records of all patients who have consulted the GUM clinic during a Pandemic Period defined to be 1 February to 30 April 2020 (90 days). We also searched and reviewed the records of all patients having consulted the clinic in two Control Periods (1 July to 28 September 2019, 90 days and 1 October to 29 December 2019, 90 days).

Results

Inclusions and Listing of the Results

Our major results are summarised in Table 1. All entries are episodes of STI to our best knowledge and belief. For example, extra-genital Herpes Simplex Virus (HSV)-2 infections would be listed, genital HSV-1 infections would be listed, while extra genital HSV-1 infections would not be listed unless the history suggested otherwise. The sexual history, physical findings, dermoscopic findings, and laboratory results were all considered in order to determine whether a disease episode was most likely to be sexually transmitted or not.

The results are listed as disease episodes. If a patient has consulted us on multiple occasions for the same disease episode, it would be counted as one.

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Rankings of Sexually Transmitted Infections	**Pandemic Period** (during COVID-19; 1 Feb - 30 Apr 2020) N# = 61	**Control Period 1** (before COVID-19; 1 Jul - 28 Sep 2019) N = 185	**Control Period 2** (before COVID-19; 1 Oct - 29 Dec 2019) N = 175	**Control Periods 1 and 2** combined (before COVID-19, 1 Jul - 28 Sep 2019, and 1 Oct - 29 Dec 2019) N = 360
(1) Herpes simplex virus-2 or -1, recurrent episode (genital or extragenital when history suggests sexually transmitted)	23 (38%)	43 (23%) PP/CP IR: 0.53, 95% CI: 0.31-0.91*	50 (29%) PP/CP IR: 0.46, 95% CI: 0.27-0.77*	93 (26%) PP/CP IR: 0.49, 95% CI: 0.30-0.79*
(2) Human papillomavirus, recurrence episode (anogenital region or other regions when history suggests sexually transmitted)	19 (31%)	28 (15%) PP/CP IR: 0.68, 95% CI: 0.36-1.26	33 (19%) PP/CP IR: 0.58, 95% CI: 0.31-1.04	61 (17%) PP/CP IR: 0.62, 95% CI: 0.35-1.06
(3) *Chlamydia trachomatis* (assumed to be serovars D-K)	5 (8%)	23 (12%) PP/CP IR: 0.22, 95% CI: 0.06-0.58*	24 (14%) PP/CP IR: 0.21, 95% CI: 0.06-0.56*	47 (13%) PP/CP IR: 0.21, 95% CI: 0.07-0.53*
(4) Molluscum contagiosum virus	2 (3%)	12 (6%) PP/CP IR: 0.17, 95% CI: 0.02-0.75*	3 (2%) PP/CP IR: 0.67, 95% CI: 0.06-5.82	15 (4%) PP/CP IR: 0.27, 95% CI: 0.03-1.15
(5) Male urethritis (pathogen unidentifiable)	2 (3%)	6 (3%) PP/CP IR: 0.33, 95% CI: 0.03-1.84	7 (4%) PP/CP IR: 0.29, 95% CI: 0.03-1.50	13 (4%) PP/CP IR: 0.31, 95% CI: 0.03-1.36
(6) Neisseria gonorrhoeae	2 (3%)	4 (2%) PP/CP IR: 0.5, 95% CI: 0.05-3.49	5 (3%) PP/CP IR: 0.4, 95% CI: 0.04-2.44	9 (3%) PP/CP IR: 0.44, 95% CI: 0.05-2.15
(7) Herpes simplex virus-2 or -1, first episode (genital or extragenital when history	1 (2%)	24 (13%) PP/CP IR: 0.04, 95% CI: 0.00-0.26*	23 (13%) PP/CP IR: 0.04, 95% CI: 0.00-0.27*	47 (13%) PP/CP IR: 0.04, 95% CI: 0.00-0.25*

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suggests sexually transmitted)				
(8) Human papillomavirus, first episode (anogenital region or other regions when history suggests sexually transmitted)	1 (2%)	19 (10%) PP/CP IR: 0.05, 95% CI: 0.00-0.33*	22 (13%) PP/CP IR: 0.05, 95% CI: 0.00-0.28*	41 (11%) PP/CP IR: 0.05, 95% CI: 0.00-0.29*
(9) Trichomonas vaginalis	1 (2%)	4 (2%) PP/CP IR: 0.25, 95% CI: 0.01-2.53	6 (3%) PP/CP IR: 0.17, 95% CI: 0.00-1.37	10 (3%) PP/CP IR: 0.2, 95% CI: 0.00-1.41
(10) Cervicitis and pelvic inflammation (pathogen unidentifiable)	1 (2%)	7 (4%) PP/CP IR:0.14, 95% CI: 0.00-1.11	11 (6%) PP/CP IR: 0.09, 95% CI: 0.00-0.63*	18 (5%) PP/CP IR: 0.11, 95% CI: 0.00-0.70*

Table 1: Incidence of the ten commonest sexually transmitted infections grouped according to pathogens where possible during the early phase of the COVID-19 pandemic and two Control Periods in a genito-urinary medicine clinic.

Total Number of Episodes of Sexually Transmitted Infections

During the Pandemic Period of 90 days, 61 episodes of STI were documented. This was significantly less than such in the Control Period 1 [185 episodes; incidence ratio (IR): 0.33, 95%CI: 0.24-0.44], Control Period 2 (175 episodes; IR: 0.35, 95%CI: 0.26-0.47), or both Control Periods combined (360 episodes in 180 days; IR: 0.34, 95%CI: 0.25-0.45).

Demographic Data and Sexual Orientations

The 61 episodes of STI during the Pandemic Period involved 59 patients. Their age ranged from 17 to 72 years. 39 (66%) were males. 20 (34%) were females. For the males, the mean age was 44.4 years (SD: 13.2 years). 32 (82%) were heterosexual, four (10%) were homosexual, and three (8%) were bisexual. For the females, the mean age was 32.7 years (SD: 11.0 years). 17 (85%) were heterosexual. Three (15%) were bisexual. All were HIV 1 and 2 Ab and P24 antigen negative.

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Such demographic variables were insignificantly different from the patients in Control Period 1, Control Period 2 and Control Periods 1 and 2 combined.

Categorisation of Results

We could categorise the frequencies of STI by syndromes such as urethritis and genital ulcers. However, since the pathogens of most patients were known, we elected to categorise according to the pathogens concerned. Furthermore, in order to facilitate our subsequent analyses, we categorised disease episodes due to HSV-2 or -1 into the first episode (due to primary infection) and recurrent episodes (due to endogenous reactivation). Similarly, disease episodes due to Human Papillomavirus (HPV) infection were categorised into the first and the recurrent episodes.

Ranking of Results

For the Pandemic Period, the rankings were (1) HSV-2 or -1 (recurrent episode), (2) HPV (recurrent episode), (3) Chlamydia trachomatis (serovars D-K), (4)-(6) molluscum contagiosum virus, male urethritis (pathogen unidentifiable), and Neisseria gonorrhoeae, (7)-(10) HSV-2 or-1 (first episode), HPV (first episode), Trichomonas vaginalis, and cervicitis and pelvic inflammation (pathogen unidentifiable).

Such ranking would be quite different for the Control Periods. Specifically, HSV-2 or -1 (first episode) and HPV (first episode) would occupy rankings (4) and (5).

Herpes Simplex Virus-2 and -1 and Human Papillomavirus

During the pandemic period, only one (4%) out of 24 patients with HSV-2 or -1 infection was a first attack. This rate was significantly lower than such in Control Period 1 (RR: 0.12, 95% CI: 0.02-0.81), Control Period 2 (RR: 0.13, 95% CI: 0.02-0.93), and both Control Periods combined (RR: 0.12, 95% CI: 0.02-0.86).

For HPV infection, during the Pandemic Period, only one (5%) out of 20 patients presented with the first attack. The clinical photo and polarised dermoscopy image are depicted in Fig. 1 respectively. This rate was again significantly lower than such in Control Period 1 (RR: 0.12, 95% CI: 0.02-0.86), Control Period 2 (RR: 0.13, 95%CI: 0.02-0.87) and both Control Periods combined (RR: 0.12, 95% CI: 0.02-0.85).

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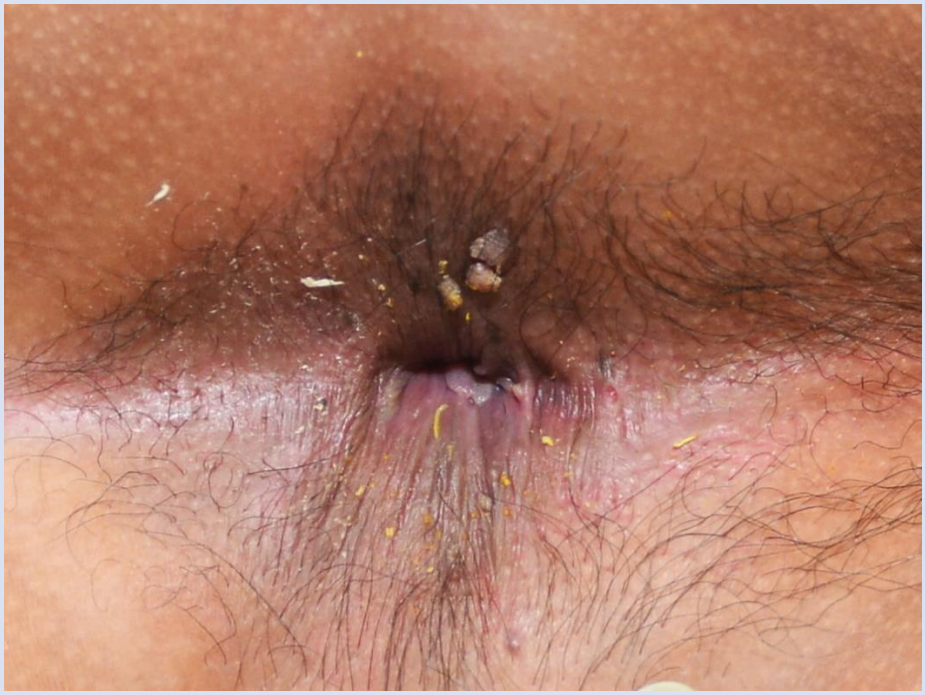

Figure 1: The only one patient presented with the first attack of human papillomavirus infection during the Pandemic Period. He was homosexual and was having perianal viral warts. All were fairly near to the anus and were not keratinised.

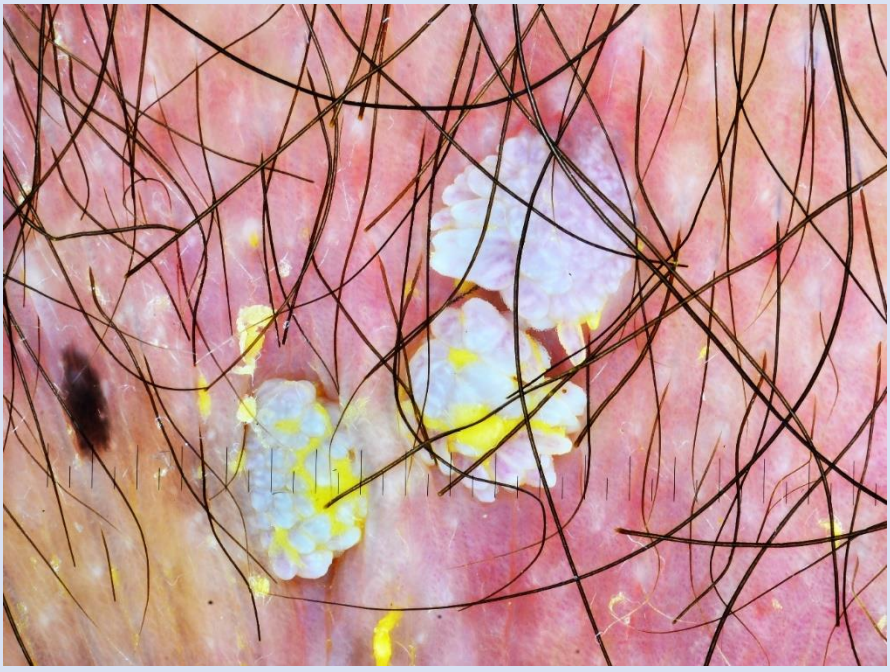

Figure 2: The same lesions as in Figure 1a depicted under polarised dermoscopy. Three polypoid lesions are seen. Within some of the compartments, fine vasculatures are

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identifiable. Near the left edge of this figure a lentigine of no clinical significance is seen. Dermoscopy not only confirmed the diagnosis for this patient. Showing this image to him might facilitate patient education and modification of his high risk sexual behaviours.

Discussion

Hong Kong is an international city. The sexual practices of the citizens vary to a broad spectrum. There is no official red-light district. However, one sex worker offering his or her service within one apartment usually known as "one-woman brothel" for a female is not illegal. Sex services are also prevalent in massage parlours and Japanese style night clubs. Teenage girls offering "compensated dating" are growing in number, and many offer sex services [3]. Many male citizens frequently travelling across the border of Hong Kong and Mainland China keep mistresses in Mainland China.

COVID-19 suddenly halted everything. After the painful lesson of SARS in 2003, citizens in Hong Kong are highly alert to epidemics and pandemics [4,5]. Within one week of the first patient diagnosed with COVID-19 (then known as Wuhan pneumonia), 98% of citizens were wearing surgical masks outside their homes and working places [6].

Most political, economic, social, cultural, and sport activities and events were subsequently delayed or cancelled. Banners showed healthcare workers advocating "We stay at work for you! You stay at home for us!" Quarantine controls kept travelling between Hong Kong and Mainland China to a bare minimum. Special permits had to be acquired for crossing the border. Otherwise, compulsory quarantine for 14 days applied.

The significant drop of the incidence of STI during the pandemic to one-third of its original level is therefore anticipated and comprehensible. Although our Pandemic Period was defined to be from 1 February to 30 April 2020, the numbers of attendees to the GUM clinic had been quite uneven. In the first four clinics, there was no attendance at all. This substantial drop in either the rate of STI transmission or the rate of consultations regarding STI is echoed by reports from the United Kingdom, Italy and Australia [7-9].

Since early March, patients were turning up in the GUM clinic again, albeit at only around 15-20% of our usual service capacity. We note from Table 1 that 38% were subsequently found by us to be having endogenous reactivation of previously sexually transmitted HSV-2 and -1, and 31% be suffering from recurrent after latent infection of HPV at the anogenital regions. Most of these patients claimed that they had been sexually inactive since the beginning of the pandemic.

For patients previously consulting us for anogenital HPV infection, around 60% was having a subsequent attack. During the pandemic, only one (5%) of the 20 patients consulting us for

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anogenital HPV infection did have the first attack. The risk ratio against the two Control Periods combined was highly significant at 0.12, with 95% CI being 0.02-0.85. For sexually transmitted HSV-2 and -1, around 65% would be consulting us for recurrent attacks. During the pandemic, it was again only one (4%) out of 24 patients presenting with primary infection. The risk ratio against the two Control Periods combined was again highly significant at 0.12, with 95% CI being 0.02-0.86.

We therefore believe that it was not merely the nature of these viruses running their natural courses of latent infection, then occasional endogenous reactivation or re-infection of neighbouring skin or mucosal surfaces. It is known that psychosocial stress can lead to relative immunocompromisation state [10,11]. We postulate that the underlying mechanism for the rise of endogenous viral reactivations was due to psychosocial stresses weakening the cell-medicated immunity in patients harbouring these viral pathogens [12-14].

Another finding warrants an explanation. If psychosocial stressors did lead to endogenous reactivations of HSV-2 and -1 during the Pandemic Period, why was the incidence for subsequent attacks of HPV-2 and -1 in the Pandemic Period (23 in 90 days) significantly lower than such in the two Control Periods (93 in 180 days) at an incidence ratio of 0.49 (95% CI: 0.30-0.79)? Similarly, for subsequent attacks of HPV, why was the incidence during the Pandemic Period (19 in 90 days) lower than such in the Control Periods (61 in 180 days), though not statistically significant?

We believe that during the pandemic, patients viewed hospitals and other healthcare facilities such as the GUM clinic as being particularly high-risk places for the transmission of SARS-CoV-2. Thus, some patients who understood that they were having secondary attacks of the same viruses might put themselves on observation until spontaneous remission or later dates for consultations. Such would explain the lower incidence rates during the early phase of pandemic.

The most important limitation in our study is that the setting was only one GUM clinic. Collaboration with other GUM clinics in the public and private sectors would have provided more powerful and reliable results. Another weakness is that we did not have comprehensive data of the types of HPV. We thus could not analyse according to the types causing anogenital warts, the types causing cervical and other cancers, and the other types.

Another weakness is the retrospective nature of the study forbidding us to assess the psychosocial states of patients. With standardised tools, we could have assessed the psychosocial status and stress of patients with viral reactivations or reinfections, to be compared with such of patients with history of HPV or HSV-2 and -1 infections but without reactivations, and with such of patients consulting us for problems entirely unrelated to STI. Furthermore, a qualitative arm could have been added in the study to analyse contents and impacts of psychosocial stress of our patients with STI during the early phase of the pandemic.

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Conclusion

During a period of 90 days in the early phase of the COVID-19 pandemic in Hong Kong, significantly less episodes of STI were diagnosed in a GUM clinic than two Control Periods each of 90 days before the pandemic. The commonest STI during the Pandemic Period were recurrent attacks of HSV-2 and -1, recurrent attacks of HPV and *Chlamydia trachomatis* infection. The risk ratios for HSV-2, -1, and HPV infections being the first episodes rather than recurrent episodes were significantly lower during the Pandemic Period than the Control Periods.

We speculate that a much lowered rate of sexual exposures during the COVID-19 pandemic might have led to significantly less STI as a whole. The accompanying psychosocial stressors might compromise cell-mediated immunity to a relative extent, leading to latent viral infections being endogenously reactivated.

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The patients in this manuscript have given written informed consent to publication of their case details.

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