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COVID-19 can lead to rapid progression of cervical intraepithelial neoplasia by dysregulating the immune system: A hypothesis

Sabeth Becker a,b, Danny Jonigk c,d, Angelina Luft a, Lena Dübbel a,b*, Christopher Werlein c, Eduard Malik a,b, Meike Schild-Suhren a,b

a University clinic of Gynaecology and Obstetrics, Carl von Ossietzky University Oldenburg, Emsstr.ße 20, 26382 Wilhelmshaven, Germany
b University clinic of Gynaecology and Obstetrics, Klinikum Oldenburg, Rahel-Straß-Str.ße 10, 26133 Oldenburg, Germany
c Institute of Pathology, Hannover Medical School, Hannover, Germany
d Member of the German Center for Lung Research (DZL), Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATh), Germany

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ABSTRACT

COVID-19 is a multisystem disease and cause of a global pandemic. Lately, cases of disease progression of HPV-infected CIN under SARS-CoV-2 infection were reported giving rise to the hypothesis of direct virus-infection induced pro-carcinogenic effect of SARS-CoV-2. We herein present a case of rapid progression from HPV-induced CIN 2 to microinvasive carcinoma within three months under COVID-19 without direct virus infection. Histopathologic evaluation, Fluorescence-in-situ hybridization and qRT-PCR against SARS-CoV-2 RNA as well as gene expression analysis were performed from the available FFPE-tissue and accompanied by an analysis of white blood cell differential. No signs of direct SARS-CoV-2 infection or COVID-19 typical alterations of cervical tissue were found. As expected, p53 decreased in expression with progression of dysplasia, while APOBEC3A and VISTA showed a decrease in expression contrary to observations in dysplasia progression. PD-L1 was expressed consistently or increased slightly but did not show the expected strong induction of expression. DNMT1 showed an increase in expression in CIN III and a slight decrease in carcinoma, while DNMT3a is consistently expressed in CIN II and decreased in carcinoma. Blood tests after COVID-19 showed substantial reduction of lymphocytes, eosinophils, T-cells, and NK-cells. Our results hint at an indirect effect of COVID-19 on the cervical neoplasm. We conclude that the immune system might be preoccupied and exhausted by the concurring COVID-19 disease, leading to less immunological pressure on the HPV-infected cervical dysplasia enabling rapid disease progression. Further, indirect proangiogenic and proinflammatory micromilieu due to the multisystemic effects of COVID-19 might play an additional role.

1. Introduction

1.1. Background

Coronavirus disease 2019 (COVID-19) is a multisystem disease leading not only to progressive lung failure but also multi organ dysfunction and coagulation disorders (Chen et al., 2020; Richardson et al., 2020) through its vasculocentric nature (Smadja et al., 2021). It is associated with high mortality and morbidity rates reaching up to 25–50% in critically ill patients (Challen et al., 2021; Chand et al., 2020). First detected in 2019 in Wuhan, China, COVID-19 rapidly spread, resulting in a global pandemic. Understanding of the pathophysiological basis of extrapulmonary organ manifestation is constantly evolving.

Cervical cancer is the fourth most common cancer diagnosis in females worldwide and the fourth leading cause of cancer death in women (Bray et al., 2018). It takes a median time of 23.5 years for cervical intraepithelial neoplasia (CIN) II-III to progress to cancer (Vink et al., 2013). Human papillomavirus (HPV) is pivotal to the development of cervical cancer and can be detected in virtually all cervical carcinomas (Walboomers et al., 1999). There are 12 oncogenic types of HPV classified as group 1 carcinogens by the IARC Monographs (International Association for Research on Cancer, 2007). Cervical cancer is a highly immunologically influenced tumor, and its risk factors are primarily associated with an increased risk of acquiring or having a compromised immune response to HPV infection (Piersma, 2011). Therefore, it is
Moreover, the close temporal relation of disease progression to RNA in the cervical smear by qPCR of 102 patients with asymptomatic et al., 2020). In addition, Ondi patient who developed a CIN I after COVID-19 infection (Vavoulidis this topic: Vavoulidis et al. reported a case of a 32-year-old HPV-positive tissue was performed. Two research teams have previously addressed lesions progress to cancer (McCredie et al., 2008). In this context, the 31% of CIN III cancer because it is treated as soon as it is detected. Generally, a median time of 23.5 years for progressive CIN II-III to cancer development is assumed (Vink et al., 2013). However, within 30 years, 31% of CIN III lesions progress to cancer (McCredie et al., 2008). In this context, the short progression time of only months in the given case is alarming. Moreover, the close temporal relation of disease progression to COVID-19 infection is striking and suggests a causal relationship. Literature research on the effects of COVID-19 disease on cervix tissue was performed. Two research teams have previously addressed this topic: Vavoulidis et al. reported a case of a 32-year-old HPV-positive patient who developed a CIN I after COVID-19 infection (Vavoulidis et al., 2020). In addition, Ondić and colleagues examined SARS-CoV-2 RNA in the cervical smear by qPCR of 102 patients with asymptomatic COVID-19 infection. Except for one case, all of them showed a negative result in qPCR (Ondić et al., 2021). Both research groups concluded that SARS-CoV-2 could directly infect cervical epithelium resulting in adverse effects and disease progression. This paper aims to set a rival hypothesis: We hypothesize that COVID-19 indirectly impacts cervical dysplasia due to a preoccupied and exhausted immune system. Consequently, immune pressure on cervical tissue under SARS-CoV-2-infection is reduced because the main focus of immune defense is elsewhere. This enables rapid progression of cervical dysplasia. We therefore employed multiple analysis to support said hypothesis. The primary endpoint of the study was the comparative analysis of dysregulated immune factors and known markers of disease progression (p53, APOBEC3A, VISTA, PD-L1, DNMT1, and DNMT3a) between the index patient and uninfected controls. Secondary endpoints were the analysis of direct virus infection on cervical tissue and the detection of abnormalities in differential blood counts. This work is intended to raise awareness about the potential impact of SARS-CoV-2 infection on cervical dysplasia and cervix carcinoma.

1.2. Case presentation

In October 2020, a 44-year-old female patient was referred to our dysplasia unit due to a PAP II D2 finding in the cervical smear. No abnormalities had been detected in previous screenings. The normal-weight patient had no previous illnesses and an unremarkable family history of cancer. She was not taking any medications, especially no hormone preparations. Detailed information on the patient’s health data is provided in the supplements. Colposcopy showed a minor lesion (cf. Fig. 1), and pathology revealed a CIN II (cf. Fig. 2). Human papilloma-virus (HPV) testing showed infection with a high-risk strain, other than 16 and 18. The patient was not HPV vaccinated. A follow-up examination in May 2021 showed rapid progress of the previously reported CIN II into microinvasive cervical carcinoma (CIN III with invasive, moderately differentiated squamous cell carcinoma. Infiltration depth 0.8 mm) (cf. Figs. 1 & 2). Thus, a LEPP-conization, including cervical curettage, was arranged with the patient. Hence, diagnosis of cervical carcinoma stage pT1a1 (3 mm) G2 L0 V0 R0 according to FIGO (Fédération Internationale de Gynecologie et d’Obstétrique) was made. At the patient’s request, the tumor board recommended a total laparoscopic hysterectomy with bilateral salpingectomy (Hillemanns et al., 2019). Three months prior to follow-up, the patient suffered from symptomatic coronavirus disease with a moderately symptomatic course. Infection was PCR-confirmed, symptoms included high fever for one week and lower respiratory tract symptoms. The coronavirus infection was completely cured after 4 weeks with no residuals.

1.3. Hypothesis

This patient’s rapid progression of cervical dysplasia into invasive cervical carcinoma within only seven months is particularly remarkable. There is only poor knowledge about the time of progression from high-grade cervical intraepithelial neoplasia (CIN II or III) to invasive cervical cancer because it is treated as soon as it is detected. Generally, a median time of 23.5 years for progressive CIN II-III to cancer development is assumed (Vink et al., 2013). However, within 30 years, 31% of CIN III lesions progress to cancer (McCredie et al., 2008). In this context, the short progression time of only months in the given case is alarming. Moreover, the close temporal relation of disease progression to COVID-19 infection is striking and suggests a causal relationship.

Literature research on the effects of COVID-19 disease on cervix tissue was performed. Two research teams have previously addressed this topic: Vavoulidis et al. reported a case of a 32-year-old HPV-positive patient who developed a CIN I after COVID-19 infection (Vavoulidis et al., 2020). In addition, Ondić and colleagues examined SARS-CoV-2 RNA in the cervical smear by qPCR of 102 patients with asymptomatic COVID-19 infection. Except for one case, all of them showed a negative

2. Materials and methods

The patient presented in this case report was diagnosed and managed in the Department of Obstetrics and Gynecology at Oldenburg University Hospital and agreed to usage of the retrieved samples and data for research purposes. This study was approved by the local Medical Ethics Committee of the Carl-von-Ossietzky University Oldenburg [ethics-vote no.: 2017–114] and complies with the ethical principles for medical research of the Declaration of Helsinki.

2.1. Direct effects of COVID-19 in cervical tissue

To evaluate direct infection of cervical cells, pathologic evaluation of microvascular architecture was performed. Moreover, quantitative real-time polymerase chain reaction (qRT-PCR), Fluorescence In Situ Hybridization (FISH) to detect SARS-CoV-2-specific RNA, and immunohistochemical staining against SARS-CoV-2 nucleocapsid and spike protein for detection of virus proteins were performed in the initial CIN 2 specimen as well as in the follow-up specimen of the microinvasive carcinoma.

2.1.1. Pathologic evaluation

Histopathologic evaluation of the material was performed by experienced pathologists at the Institute of Pathology at Hannover Medical School. Particular attention has been paid to endothelial cell disruption and microvascular alterations, both have previously been demonstrated in several other organ systems and are an indication of infection by SARS-CoV-2 (Varga et al., 2020).

2.1.2. SARS-CoV-2 virus detection

3–4-μm sections were cut from formalin-fixed paraffin-embedded specimens (FFPE) samples that were deparaffinized in xylene and then dehydrated with 100% ethanol.

![Fig. 1. Colposcopy of the initial CIN II dysplasia before COVID-19 (Panel A) and the progression towards the microinvasive carcinoma (panel B) with green filter (panel C).](image-url)
Immunohistochemical detection of SARS-CoV-2 proteins was performed on tissue sections from FFPE embedded tissue using IgG fractions of a rabbit anti-SARS-CoV-2 spike protein antiserum (40150-R007, Sino Biological, Peking) and a monoclonal mouse anti-nucleocapsid antibody (40143-MM05, Sino Biological, Peking) at a dilution of 1:100 and detected using DAB detection kit (760-500, Ventana Medical Systems, Inc., Tucson, USA).

Fluorescence in situ hybridization (FISH) was performed using the same samples as described for immunohistochemistry using the Hulu FISH probe against SARS-CoV-2 nucleocapsid protein (R-0101, MetaSystems, Altusheim, Germany) at a 1:100 dilution and detected using DAPI/Dura-Tect-Solution ultra (LOT MT-0008, Zytomed Systems GmbH, Berlin, Germany). For SARS-CoV-2 qPCR detection, RNA was extracted from FFPE tissue using a Maxwell LEV RNA FFPE Purification Kit (Promega GmbH, Walldorf, Germany) on an AmpliPrep 16 IVD instrument (Promega GmbH) or with the Maxwell® 16 LEV RNA FFPE Purification Kit (Promega GmbH, Waldorf, Germany) on the Maxwell® 16 IVD instrument (Promega GmbH) or with the ReliaPrep™ FFPE Total RNA Miniprep System (Promega GmbH) according to the manufacturer’s instructions. RNA samples were stored at −80 °C until further processing. TaqMan™ Fast 1-Step Master Mix (Thermo Fisher Scientific GmbH, Dreieich, Germany) was used for the qualitative detection of the E gene (encoding envelope protein) of lineage B beta-coronavirus (B-βCoV) by a primer (0.4 μM) and probe (0.2 μM) set labeled with fluorescent reporters and quencher dyes. TaqMan® Exogenous Internal Positive Control reagents (Thermo Fisher Scientific GmbH, Dreieich, Germany) served as internal PCR controls. RT-PCR was performed as previously described (Stillfried et al., 2021; Remmelink et al., 2020). Briefly, RNA was reversely transcribed (50 °C for 10 min) and amplified with the reaction mixture at 95 °C for 30 s and followed by 45 cycles of 95 °C for 3 s and 58 °C for 30 s. Amplirun® SARS-CoV-2 RNA control (Bestbion dx GmbH, Cologne, Germany) provided with 13000 viral RNA copies μl-1 was used to determine the number of viral RNA copies μl-1.

2.2. Assessment of Indirect effects of COVID-19 on cervical tissue via gene expression analysis

To assess indirect effects of COVID-19 on cervical tissue due to a dysregulated immune system, quantitative real-time polymerase chain reaction (qRT-PCR) was performed:

2.2.1. Quantitative real-time polymerase chain reaction

RNA extraction from FFPE samples was performed after removing paraffin with xylene and rehydration of the tissue with 99.8% and 75% ethanol. Cell lysis was performed using Digestion Solution (prepared in-house), Proteinase K (1245680100, Merck/Sigma Aldrich), and β-mercaptoethanol (M6250–10 ML/8057400005, Merck/Sigma Aldrich) and incubated overnight at 55 °Celsius in a thermal shaker. Ribonucleic acid (RNA) was isolated using a solution of Na-acetate (pH 5.5) (AM9740, ThermoFisher Scientific), Aqua Roti-Phenol (pH <4) (A980.1, Carl Roth), and chloroform (288306–100 ML, Sigma Aldrich). After phase separation, to precipitate the RNA, the aqueous supernatant was mixed with glyceron and isopropanol and incubated for one hour at room temperature. After centrifugation, quantitative and qualitative determination of RNA was performed using UV/VIS spectrophotometry (BioDrop spectrophotometer).

Expression levels of APOBEC3A, APOBEC3B, p53, PD-L1, VISTA, DNMT1, and DNMT3α mRNA were determined by quantitative real-time polymerase chain reaction (qRT-PCR). For detailed parameters, see...
Table 1
qRT-PCR conditions.

| Gene      | Primer concentration [nM] | cDNA concentration [ng] | Annealing temperature [°C] |
|-----------|---------------------------|-------------------------|---------------------------|
| GAPDH     | 300                       | 75                      | 48                        |
| RPLP0     | 250                       | 75                      | 48                        |
| APOBEC3A  | 150                       | 75                      | 48                        |
| APOBEC3B  | 400                       | 50                      | 46                        |
| p53       | 450                       | 50                      | 60                        |
| PD-L1     | 300                       | 75                      | 48                        |
| VISTA     | 250                       | 50                      | 50                        |
| DNMT1     | 450                       | 25                      | 48                        |
| DNMT3a    | 450                       | 75                      | 50.8                      |

Table 1.
Reaction was performed with SYBR® Green Master Mix (BioRad, USA). The samples were analyzed in duplicates or triplicates using the CFX Connect Real-Time System (BioRad, USA). Analysis of qPCR was performed using the instrument software (BioRad CFX Maestro). GAPDH and RPLP0 were used as housekeeping genes for relative quantification.

3. Results

3.1. Direct effects of COVID-19 in cervical tissue

Upon histopathological evaluation, no salient architectural disturbance (e.g., microthrombi) of the smaller vessels or a lymphocytic inflammatory infiltrate as an indication of direct viral infection in the cervical tissue could be visualized in the specimens.

No evidence of residual viral RNA fragments or SARS-CoV-2 spike, or nucleocapsid protein was found in the available material via Fluorescence In Situ Hybridization (FISH), qRT-PCR, and immunohistochemistry.

3.2. Indirect effects of COVID-19 on cervical tissue

qRT-PCR-based analysis of gene expression in the cervical tissue revealed a decrease in APOBEC3A, p53, and VISTA expression with progression of dysplasia. DNMT1 was expressed differently during progression, with an increase of expression from CIN II to CIN III but a decrease of expression in the carcinoma compared to both CIN II and CIN III. DNMT3a showed a stable expression from CIN II to CIN III with a decrease of expression only in the invasive carcinoma. However, PD-L1 showed a consistent to slightly increased expression during the course of the disease, while APOBEC3B was not detectable in any sample. (cf. Fig. 3).

Two patients with disease progression from CIN I to invasive carcinoma or from CIN II to CIN III respectively without SARS-CoV-2 infection served as uninfected control samples (Fig. S1 and S2). The uninfected samples showed an increase in the expression of APOBEC3A, APOBEC3B, and PD-L1 expression with progression of dysplasia. VISTA gene expression levels showed different behaviour in both control patients, with one displaying a slight increase and the other a decrease in levels. DNMT3a increased in both control patients with progression of dysplasia, while DNMT1 could not be detected in the CIN III/G2 carcinoma for technical reasons.

4. Discussion

We herein presented a case of rapid progression from HPV-induced CIN 2 to microinvasive carcinoma within three months under COVID-19 in a 44-year-old woman. Despite no signs of direct virus infection, we could show a dysregulation in immune factors and unusual courses of known markers of disease progression compared to uninfected controls hinting at signs of indirect effects of the infection on the immune system favoring disease progression.

4.1. Direct effects of COVID-19 in cervical tissue

The cervical specimen of the herein-reported case showed no evidence of direct SARS-CoV-2 infection: No conspicuous architectural disturbance of small vessels nor evidence of virus-specific RNA fragments or detectable virus protein were found. These findings are in line with previous reports of Ondic and colleagues reporting only one patient out of 23 with weak positivity in qRT-PCR (Ondić et al., 2021). In contrast to said study that focused on asymptomatic patients, the patient in the present study showed a clinically manifest infection of SARS-CoV-2 with supposedly higher levels of virus RNA to be expected (Fajnzylber et al., 2020). Still, we did not find any signs of direct virus infection of the available cervical tissue questioning a direct infectibility of the cervix and underlining indirect effects of the viral infection on disease progression.

Another aspect speaking against the hypothesis of direct infection of cervical cells with SARS-CoV-2 is the fact that the required host-receptor angiotensin-converting enzyme 2 (ACE2) for virus entry is hardly expressed by cervical epithelial cells no protein expression detected, RNA expression 0.6 nTPM (Thul et al., 2017), Human Protein Atlas) and is thus, in contrast to the respiratory and gastrointestinal tract as well as the kidney, not considered as a high-risk tissue for SARS-CoV-2 infection (Zou et al., 2020). Given, that infection of cervical epithelial cells with SARS-CoV-2 is unlikely, infection via endothelial cells or migrated macrophages, both populations known to be readily infected by SARS-CoV-2 (Junqueira et al., 2021; Varga et al., 2020) cannot be ruled out. Studies on a larger scale, such as the one announced by Vavoulidis et al. (Vavoulidis et al., 2020), remain to be seen.

4.2. Indirect effects of COVID-19 on cervical tissue

We found several indications that SARS-CoV-2 infection has effects on the immune system.

Apolipoprotein B mRNA editing enzyme catalytic polypeptide 3 (APOBEC3) proteins serve as antiviral defence against RNA virus infections such as HPV (Sawyer et al., 2004). Therefore, the proteins...
APOBEC3A and APOBEC3B are expected to be upregulated in HPV-positive patients as the disease progresses. This is observable in our control patients with progressing CIN dysplasia without SARS-CoV-2 infection (Fig. S1 and S2) despite minor individual differences, while the index patient showed a decreased expression of APOBEC3A with progression of dysplasia. The absence of high expression of a virus defense mechanism despite apparent virus infection of the cervix supports our hypothesis of an altered immune response to cervical infection with HPV during clinically manifest COVID-19 disease.

Several studies have investigated the expression of PD-L1 in cervical cancer. In 34–96% of peritumoral dendritic cells of cervical cancer tissues, PD-L1 expression was detected (Enwere et al., 2017; Yang et al., 2013), while regular cervical tissue displayed a low-level expression of PD-L1 of 6,82% in dendritic cells (Chen et al., 2016). During high immune pressure, as seen in cervical neoplasms (Piersma, 2011), increasing expression of PD-L1 is expected in order to evade the immune system. This effect is observable in the control specimens with increasing PD-L1 levels, whereas the herein-reported case showed a stable up to a slightly increased expression of PD-L1 during the course of the disease. These findings suggest lowered immune pressure as a potential sign of an exhausted immune system due to concomitant higher immune pressure in the epicentres of the SARS-CoV-2 infection.

VISTA (V-domain immunoglobulin suppressor of T cell activation) is an immune checkpoint inhibitor involved in the regulation of T cell activity and expressed on T cells and other myeloid cells (mainly monocytes, macrophages, and neutrophils (Lines et al., 2014)). VISTA has been detected in both cervical squamous cell carcinoma and clear cell carcinoma of the cervix (Zong et al., 2020). The structural similarity to PD-L1 leads to the assumption that there is likewise an increased expression in the case of a malignant event. In line with our findings on PD-L1 and our hypothesis of lower immune pressure in the cervix during COVID-19, we detected a reduced expression of VISTA in the index patient.

p53 (tumour suppressor protein 53) is a transcription factor. It is often referred to as the ‘guardian of the genome’. After DNA damage, it regulates the expression of genes involved in cell cycle control, induction of apoptosis, and DNA repair (Besse et al., 1992). P53 is inhibited by the HPV oncogene E6 (Garima, 2016). Therefore, with increasing HPV oncoprotein E6, p53 expression is usually more and more inhibited, leading to progressing dysplasia. As expected, p53 was decreased in the presented case suggesting that the general carcinogenesis pathway of HPV-associated cervix carcinoma proceeds in the same way as in comparative studies without concomitant symptomatic COVID-19.

Another aspect of COVID-19 effects discussed is the change in DNA methylation. Several studies showed that COVID-19 can lead to hyperbut especially hypomethylation of promoters of several genes (Mehammad, 2021; Konigsberg, 2021; Balnis et al., 2021) by DNA-methyltransferases (DNMTs). Mohammad and colleagues could show that DNMT1, 3a, and 3b are significantly decreased in SARS-CoV-2 transfected cells. Interestingly, HPV also changes DNA methylation. Several studies showed that COVID-19 can lead to hypermethylation and might reduce DNMT expression in the cervix. However, the expected increase of DNMT3a expression, which is observable in both control patients, cannot be observed in the index patient, giving rise to the hypothesis that SARS-CoV-2 infection has a global impact on DNA methylation and might reduce DNMT expression in the cervix. However, our samples were taken three months after SARS-CoV-2 infection and showed no signs of direct virus infection, limiting the data interpretation. Further investigations in larger cohorts during and shortly after COVID-19 are needed to evaluate this aspect.

Blood tests three months after COVID-19 showed a substantial reduction of lymphocytes (14%, abs. 0.79x10⁹/L; norm: 22–49%, 1.05–2.87x10⁹/L), eosinophils (0%, norm: 1–5%), T-cells (596/µL, norm: 700–2100/µL), NK-cells (57µL, norm: 90–600µL), and thrombocytes (137x10⁹/L; norm: 171–388x10⁹/L); a frequently described residual after COVID-19 (Bermejo-Martin et al., 2020; Dao et al., 2020; Ruan et al., 2020; Zong et al., 2021) and a sign of a high turnover of immune cells. A low number of remaining immune cells can fuel the progression of malignant events (Castelino et al., 1997), especially in immune-sensitive tumors, supporting our thesis of an exhausted immune system due to COVID-19 leading to disease progression.

On a further note, Demirbaş and colleagues report a case of HPV-induced mucocutaneous verrucae vulgaris, which regressed spontaneously within one month after symptomatic SARS-CoV-2 infection suggesting a COVID-19-induced excessive inflammatory response to the herpes virus infection with a consecutive paradoxical immune response (Demirbaş et al., 2021). On the contrary, in the case presented, symptomatic COVID-19 lead to a disease progression (in the malignant counterpart) of HPV-induced tumors. We therefore, consider a paradoxical immune reaction due to COVID-19, but this reaction seems not to be consistent or specific to COVID-19.

Nevertheless, we do not assume a general positive effect of COVID-19 on HPV-infected tissue. Contrarily, an immune activation could have been induced by a wide variety of triggers. An immune activation due to infection certainly depends on the severity of COVID-19 and the immune system’s capacities. A rather mild infection could activate the immune system but does not demand it in excess, thus avoiding exhaustion of the immune system potentially resulting in a favorable role of COVID-19 on HPV-induced tumors. On the other hand, a more severe cause of disease might have an adverse effect on (herpes-)virus- or immunologically-induced dysplasia because the immune system is quickly utilized and exhausted.

4.3. Limitations

Despite the detailed analyses performed, our hypothesis cannot be proven based on data from one index patient. Rather, this study is intended to be a stimulus for scientific discourse on the potential impact of COVID-19 on cervical dysplasia and to raise awareness among the scientific community to identify similar courses of disease and recruit them into larger studies.

Further, as at the time of infection in 2020 no SARS-CoV-2 vaccine had been developed, no conclusions can be drawn about the potential impact of SARS-CoV-2 vaccination on immunologic aspects of cervical dysplasia.

4.4. Summary

In summary, our findings endorse the hypothesis that COVID-19 negatively impacts cervical dysplasia due to lower immune pressure on cervical dysplasia by means of an altered gene expression pattern and an exhausted and depleted immune system without direct SARS-CoV-2 infection of the cervix. These findings are interesting in clinical practice as (I) patients with early cervical dysplasia should be assessed not only for known diseases or treatments leading to immunosuppression (e.g., COVID or immunosuppressive therapy for CED) but also for immunological diseases such as COVID-19 and (II) if present shorter control intervals should be considered.

5. Conclusion

Even though the patient showed a moderate symptomatic infection, there was no evidence of direct infection of cervical cells by SARS-CoV-2. Instead, the results suggest that COVID-19 indirectly impacts cervical dysplasia due to a preoccupied and exhausted immune system favouring disease progression.
