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Original Article

Assessment of CXCL10 and vitamin D in patients with persistent pityriasisrosea during COVID-19 pandemic

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Abstract

Background Pityriasisrosea (PR) is an exanthematous disorder accompanied by systemic recurrence of HHV 6 and/ or 7.

Objective To explain the link between levels of vitamin D and CXCL10 in persistent PR during COVID-19.

Methods The study encompassed 25 patients (10 males and 15 females, age range: 10–40 years) with persistent PR more than 12 weeks and 25 control subjects (12 males and 13 females, age range: 11- 38 years) examined in the medical Excellence center, Dermatology Outpatient Clinic, National Research Center, Egypt between November 2020 and March 2021. Blood samples were collected from controls and persistent PR patients for more than 12 weeks, 15 days later after topmost clinical symptoms. Assessment of serum CXCL10 was done by ELISA kit. Vitamin D was determined using the chemi-luminescence technique.

Results A student unpaired T- test was done at $P<0.05$ illustrating a significant increase in levels of CXCL10 while a significant decrease in levels of vitamin D in the sera of both male and female patients in comparison to control ones.

Conclusion Our study provided evidence that circulating CXCL10 is elevated in persistent PR patients as well as in COVID-19 where PR is one of clinical symptoms of coronavirus. This highlights the immunological response in PR and contributes to a clear explanation of cutaneous defense mechanism. Vitamin D showed a significant reduction in persistent PR patients and has been shown to be safe and guard against acute respiratory infections as in COVID-19.

Key words
Vitamin D, Pityriasisrosea, COVID-19, CXCL10, chemokine, infection.

Introduction

PR is an exanthematous disorder accompanied by systemic reactivation of human herpesvirus 6 and/or 7.[1] Usually starts by a solitaryherald patch followed by small lesions on cleavage lines of the trunk (Christmas tree pattern) 2 weeks later. Time interval is variable though habitually steadily fades within 4 weeks. Regular clustering of cases, constitutional symptoms, and nearly complete lack of frequent incidents explain the infectious cause of

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disease.[1] The enormous positivity of HHV-6/7, variable severity of eruption, low human-to-human spread rate, its occurrence and relapses in situations of changes in immunity altogether elucidate why PR is a clinical demonstration of HHV-6 and/or7 reactivation.[2,3] It was established that in some cases of COVID-19, reactivation of viral infections as HHV-6, HHV-7, and EBV is spotted.[4] Immunohistological studies indicated existence of T cells and Langerhans cells in dermal infiltrate of PR lesions, signifying cell-mediated immunity role in the disease[5].It was demonstrated that, the δ- chemokines, and IL-22, produced by Th17 cells, are elevated in sera of active PR patients,[1,6] contribution of these chemokines via its antimicrobial defense, proposes an active immune reaction in PR. Moreover, TH17 has a dual role in PR as well as in COVID-19 since it contributes to cytokine storm in pulmonary viral infection.[7]

Vitamin D is steroid hormone involved in various metabolic processes in utmost tissues. Its deficit leads to infertility, immune and cardiovascular disorders and occurrence of some malignancies.[8-10] Formation of its active form is controlled by Ca, P, parathyroid hormone as well as liver and kidney hydroxylases activity. Generally, above 90% of VD originates from skin photosynthesis due to sun exposure.[11-13]

Vitamin D3 down regulates production of inflammatory cytokines, as TNF-alpha and IL6 and increases inhibitory cytokines thus reducing COVID-19. Its deficiency contributes to acute respiratory distress syndrome and is a pathogenic factor in coronavirus.[14-18]

CXCL10/IP-10 is an IFN-inducible chemokine produced via various cells e.g. neutrophils inducing chemotaxis, apoptosis and angiogenesis.CXCL10 is up regulated by IFN-γ, and is increased in PR patients mainly in final phase of the disease since it is considered to be the chief cytokines that distinguish between PR and healthy individuals.[4]

CXCL10 has a conventional role in COVID-19-related cytokine storm and ARDS, therefore, CXCL10 is an excellent predictor for the progression of COVID-19, due to the positive and significant correlation with the viral load.[19-21]

So, aim of this research is assessing the link between vitamin D and CXCL10 in persistent PR during COVID-19.

Methods

Patients and Controls: The study encompassed 25 patients (10 males and 15 females, age range: 10–40 years) with persistent PR more than 12 weeks. The inclusion criteria were patients seeking skin care in the medical Excellence center, Dermatology Outpatient Clinic, National Research Centre, Egypt between November 2020 and March 2021 and gave signed an informed consent to provide blood samples for laboratory investigations after confirming PR diagnosis. 25 healthy subjects, sex- and age matched (12 males and 13 females, age range: 11–38 years), were enrolled as control. Each participant signed an informed consent to the study. Exclusion criteria were all PR patients who received immunosuppressive drugs with atypical rash or infectious diseases.

Serum Samples: Blood samples from persistent PR patients for more than 12 weeks were collected after 15 days (at postacute phase) related to the topmost of the clinical manifestations. Blood samples were assembled in centrifuge tubes without additive andleft to clot at room temperature for 30 minutes before centrifugation (1000 ×g, 15 minutes); the serum was stored at -80^0C until analyzed.

Evaluation of serum CXCL10 and citamin D: Serum chemokines, CXCL10 (IP-10), was measured by ELISA kit as previously described[22]. Vitamin D was determined using the Chemilumine Scence Technique (ARCHITECT 25-OH Vitamin D, Abbott Diagnostics, IL, USA).

Statistical analysis

Statistical analysis was done using unpaired student T-test, where significant difference at $p<0.05$. Data are expressed as Mean±S.D.

Results

Table 1 shows that in a group of 50 subjects (25 patients and 25 control), a study was carried out to estimate the levels of vitamin D and CXCL10 in subjects suffering from persistent pytriasis rosea. A student T test was carried out for 2 independent means at $P<0.05$ which illustrated a significant increase in levels of CXCL10 while a significant decrease in levels of vitamin D in the sera of both male and female patients in comparison to control ones.

Discussion

The present study declared that in a group of 50 subjects (25 patients and 25 control), patients had persistent pytriasis rosea with significant increase in levels of CXCL10 while a significant decrease in levels of vitamin D in the sera of both male and female in comparison to control ones.

CXCL10 in pytriasis rosea: CXCL10/IP-10 is an IFN-inducible chemokine playing chief role in controlling viral replication being extremely up-regulated by type I & II IFN and strongly endorses chemotaxis of NK, CD4+, and CD8+ T cells.[23-25] CXCL10 is up-regulated by IFN-γ, since an intra-subject positive association concerning IFN-γ and IP-10 was found and both were significantly elevated in PR patients versus control. CXCL10 levels elevate chiefly in final phase of disease ($T2$), though IFN-γ has a chief raise in PR "intermediate" phase.

HHV-6 and 7 in pytriasis rosea: The correlation between PR and HHV-6 & 7 has been well recognized,[4,26] where they are active in its early stage. In addition, the plasma load of HHV-6 & 7, an indicator of viral replication, is allied with occurrence of systemic symptoms along with decline of humoral neutralizing response against HHV-7, additionally proposing that PR is owing to endogenous reactivation of HHV-7 or 6 infection.[27]

Table 1 Comparison between case and control groups in levels of vitamin D and CXCL10 in Pytriasisrosea.

Parameter	*Min*	*max*	*Mean + S.D.*	*T value*	*P value*
Vitamin D Case	M: 5 F: 8	M: 24 F: 21	M: 13.4+ 5.02 F: 11.4+3.96	M: 6.05 F: 5.09	M:0.00001 * F:0.00004 *
Vitamin D Control	M: 17 F: 16	M: 30 F: 27	M: 23.5+3.69 F: 21.4+4.36		
CXCL10 Case	M: 15 F: 14	M: 29 F: 30	M: 21.9+4.37 F: 22.1+5.92	M: 10.5 F: 6.83	M:0.00001 * F:0.00001 *
CXCL10 Control	M: 5 F: 4	M: 12 F: 11	M: 8.27+2.14 F: 7.5+2.46		

M: male, F: female S.D.: Standard deviation, CXCL10: chemokine 10.
* There is a significant difference by using unpaired student T-test at $p < 0.05$.
Data is expressed as Mean±S.D.

Typical eruptions of pityriasisrosea last 6–8 weeks, even though intervals as long as 5 months and as short as 2 weeks have also been reported.[28,29] Only 2.8% of patients relapse [28] Yet, Halkier-Sørensen[30] stated a patient with recurrences detected yearly for 5 successive years. After a period of a few months or many years' second attacks of pityriasisroseahappen.[28] Though, authors suggested that relapse rate was possibly an underestimation as rarely the doctor who made the original diagnosis would be the same who witnessed the relapse.[26] This may explain deficit of reports on several relapses of pityriasis rosea in literature.

Vitamin D in pytriasis rosea: Regarding Vitamin D, current results showed significant reduction in male (-75.4%) and female (-87.72%) subjects. Deficiency of vitamin D is a chief complain in all ages,[31] usually above 70 years, due to diminished sun exposure and cutaneous synthesis.[32] 75% of institutionalized people are brutally vitamin D deficient.[33]

Vitamin D supplementprotects against acute respiratory infections.[18] Its deficit doesn't allow macrophages to mature, produce lysosomal enzyme acid phosphatase and to secrete H2O2, a task vital to their antimicrobial function.[34] Toll-like receptors are fundamental in innate immune response recognizing molecules related to pathogens and produce cytokines, antimicrobial peptides (cathelicins and defensins) and reactive oxygen species. They either affect or become affected by vitamin D receptor induction.[35] Vitamin D inhibits macrophages from producinginflammatory cytokines by modulating their response.[17]

COVID-19 and pytriasis rosea: COVID-19 is an ongoing viral pandemic spreading all over the world caused by SARS-CoV-2. Pytriasis rosea is one of its clinical manifestations where skin manifestation has been reported in 0.2% of COVID-19 patients in China[36], and 18 out of 88 patients from Italy[37]. The utmost frequently stated features are exanthomatous rash, urticaria, chickenpox like vesicles and petechiae.[38-40]

COVID-19 infection in PR showed a chest CT with patchy ground glass infiltration at periphery and base of both lungs. Although pityriasis rosea was accompanied by reactivation of herpesvirus 6 and 7; some cases of COVID-19 revealed its contribution in reactivation of viral infections as HHV-6 and HHV-7.[4,41]

Furtherstudies discovered the role of some chemokines as IL- 22, a cytokine produced by Th17 cells and its role in the cytokine storm in pulmonary viral infection (Dandan Wu, 2020) which are also elevated in sera of active PR patients.[6,7] CXCL10 an IFN-inducible chemokine,may be also be the key chemokine related to the cytokine storm of COVID-19 infection owing to its direct relation to the viral load and being significantly expressed during and after the infection.[20,21]

Vitamin D3 down regulates production of inflammatory cytokines, as TNF-alpha and IL6 and increases inhibitory cytokines thus reducing COVID-19. Its deficiency contributes to acute respiratory distress syndrome (one of the main clinically relevant consequences in patients with COVID-19) and is a pathogenic factor in coronavirus. Therefore, it is advocated that vitamin D may be a potential therapeutic approach to warfare the incidence of cytokine storm and its induced ARDS due to its defensive action by down regulating production of inflammatory cytokines, thus reducing the risk of COVID-19.[14-18] In both Switzerland and Italy, where there is high number of COVID-19 cases with high risk for morbidity and mortality, vitamin D levels in nursing homes are 23 nmol/L and 76% of women above 70 years have levels below30 nmol/L respectively.[3]

CXCL10 and vitamin D both are the chief factors linking PR to COVID-19 and explaining the reason why some cases with COVID-19 infections have skin manifestation in the form of PR.

Conclusion

This study examined the chemokine CXCL10 and Vitamin D levels in PR, indicating that circulating CXCL10 is increased in persistent PR patients as well as in the newly pandemic COVID-19. This underscores the immunological response in PR and contributes to a clear explanation of cutaneous defense mechanism. Vitamin D showed significant reduction in persistent PR patients and guards against acute respiratory infections. It is advised to accomplish more researches concerning vitamin D and CXCL10 levels in persistent PR patients with diverse grades of disorder severity though they are expected to be the therapeutic approaches for COVID-19.

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