



Covid Tongue as a Useful Early Clue in the Daily Clinical Practice



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Abstract

Background: Clinical features of COVID-19 include features directly related to infection, but the clinical spectrum of COVID-19 is also a consequence of the spectrum of the immune responses to the. Since the pandemic in 2020, many studies and observations were made about certain immunological manifestations and relevant physical signs including strawberry tongue. **Objective:** The purpose of the present study was to assess the prevalence of the strawberry tongue in patients with PCR positive COVID-19 infection and to determine the association between this finding and other manifestations of the disease. **Methodology:** This study was a prospective case control study, fifty patients who attended the outpatient internal medicine clinic in the period from June 2023 to July 2023 and tested positive for COVID-19 were collected. The presence of strawberry tongue was documented along with other clinical and laboratory manifestations. The results were compared to fifty cases who presented with acute febrile illness and tested negative for COVID-19. The results were analyzed using SPSS 23 and P value less than 0.05 was considered statistically significant. **Results:** The study revealed that 78.0% (30 patients) of PCR positive patients had strawberry tongue, this sign appeared earlier in the course of the illness (the first two days). About 80.0% of patients with strawberry tongue sign had vomiting and diarrhea (60.0% of the overall population study). Patients with strawberry tongue had excellent response to systemic corticosteroids in the form of improved fever, fatigue and gastrointestinal symptoms so the presence of this sign may be an indirect clue for early initiation of steroid therapy. **Conclusion:** In conclusion, a large proportion of patients with fever and positive COVID-19 PCR test have strawberry tongue. It is more common in young age group and it is significantly associated with the occurrence of vomiting and diarrhea. [*Bangladesh Journal of Infectious Diseases, June 2024; 11(1):9-15*]

Keywords: Covid 19; Kawasaki disease; strawberry tongue

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Introduction

Coronaviruses are enveloped, single genome segment, positive strand RNA viruses that belong to the Coronaviridae family. Although most coronaviruses cause mild flu like symptoms, 2 beta coronaviruses (severe acute respiratory syndrome

coronavirus and Middle East respiratory syndrome coronavirus) have resulted in more widespread and serious epidemics in 2002 and 2012, respectively¹.

The Chinese new year Festival on January 25, 2020 was an unforgettable memory to all Chinese who were urged to stay home for many weeks due to the

outbreak of a novel viral illness that was highly similar to the coronavirus (CoV) that caused an outbreak of severe acute respiratory syndrome (SARS) in 2003; thus, it was named SARS-CoV-2 by the World Health Organization (WHO) on February 11, 2020, and the associated disease was named CoV Disease-19 (COVID-19)². The epidemic started in Wuhan, China, and quickly spread throughout the entire country and to near 50 others all over the world. As of March 2nd, 2020, the virus resulted in over 80,000 confirmed cases of COVID-19 and over 3,000 patients who died. WHO warned that COVID-19 is “public enemy number 1”³.

The estimated mean incubation period of SARS-CoV-2 is 1-14 days, mostly 3-7 days based on a study of the first 425 cases in Wuhan⁴. However, a study on 1,099 cases shows that the incubation period was 3 days on average and ranged from 0 to 24 days⁵. Corona virus had been previously considered non lethal to humans, causing nearly 15% of common cold cases⁶. However, in the 21st century, highly pathogenic human coronavirus strains were reported twice, *i.e.*, SARS-CoV and MERS-CoV, which caused an outbreak originally in China in 2003 and Saudi Arabia in 2012, respectively with high morbidity and mortality. Therefore, the current COVID-19 is the third CoV outbreak in the recorded history of humans.

On January 24 the first clinical study on the disease reported that, out of 41 patients with confirmed cases, only 21 had direct contact with the Wuhan seafood market that was considered the starting site of the infection from an unknown animal source. On 20th of January 2020, WHO announced the outbreak a universal health emergency^{7,9}. It has been known that both SARS-CoV and MERS-CoV originated from bats and were transmitted to humans via civet cats and camels, respectively. Through a phylogenetic comparison of COVID-19 virus with other Coronaviruses, bats were also considered the native host of SARS-CoV-2⁸.

Fever is often the initial symptom of COVID-19, which may be accompanied by no symptom or other symptoms such as dry cough, shortness of breath, myalgia, headache, sore throat, rhinorrhoea, diarrhoea, nausea, and vomiting. Some patients experienced dyspnoea with or without hypoxia one week after the onset of the disease. In severe cases, patients rapidly progressed to develop acute respiratory syndrome, septic shock, metabolic acidosis, and coagulopathy. Patients with fever and/or respiratory symptoms, even without chest imaging abnormalities, should be screened for the virus for early diagnosis¹⁰.

A demographic study conducted in China in December 2019 showed that the percentages of the reported symptoms were 98% for fever, 76% for dry cough, 55% for dyspnoea, and 3% for diarrhoea and 8% of the patients required ventilation support¹¹. Most of the patients had normal or low numbers of peripheral white blood cells (especially lymphocytes) at the early stage.

For example, lymphopenia with white blood cell count $< 4 \times 10^9/L$ including lymphocyte count $< 1 \times 10^9/L$, and elevated aspartate aminotransferase levels were found in 1,099 COVID-19 patients. Serum levels of liver and muscle enzymes and myoglobin were elevated in some patients, and C-reactive protein and erythrocyte sedimentation were increased in the blood of most patients. In patients with more severe cases, D-dimer levels, which is a fibrin degradation product found in the blood, were elevated, and lymphocyte count was progressively decreased¹².

The detection of SARS-CoV-2 RNA by reverse-transcriptase polymerase chain reaction (RT-PCR) was used as the most important criteria for the diagnosis of COVID-19. However, due to the high false-negative rate, which may accelerate the spread of the epidemic, clinical features were started to be used for diagnosis (diagnosis was no longer dependent on RT-PCR only) in China on February 13, 2020. A similar situation also occurred during the pandemic of SARS¹³.

While respiratory and gastrointestinal complications were the main manifestations of coronavirus disease 2019 (COVID-19), many more manifestations became apparent as the pandemic progressed. Lingual involvement has been extensively reported in COVID-19 patients. The most primary features are chemosensory disorders, such as smell and taste problems. These complications frequently happen during many viral infections, such as influenza¹⁴. Moreover, COVID-19 has been attributed to a Kawasaki disease-like manifestations with glossitis, also called red strawberry tongue. Furthermore, the tongue can also be involved as a component of angioedema in the setting of COVID-19 infection¹⁵.

Most of the oral manifestations and taste disturbances subsided spontaneously. Nevertheless, some may need special treatment like corticosteroids¹⁶. In Iraq, at the early stages of COVID-19 pandemic, there was complete reliance on WHO for supplying PCR testing kits but later, Kimadia (the state company for drug and medical appliances, Iraq ministry of health), started taking the lead together with private labs¹⁷. the

availability and the cost remains an obstacle while managing large number of patients with acute febrile illness so useful clinical and laboratory clues to Covid-19 patients is very useful in the crowded daily clinical practice with limited resources. The aim of the study is to evaluate the prevalence of strawberry tongue in COVID-19 patients who were proved positive by PCR test, assess the association of this clinical sign with other manifestations of the disease and its relevance to the management and prognosis of the illness.

Methodology

Study Design and Population: This study was a prospective case control study. Fifty patients with PCR positive COVID-19 infection who attended the outpatient clinic in the period of June to July 2023 were assessed for the presence of strawberry tongue in the early stages of the disease (first two days of the onset of the symptoms). Patients who were known to have anemia, vitamin B deficiency or Kawasaki disease were excluded from this study.

Study Procedure: The findings were compared to other fifty patients who presented with acute febrile illness and tested negative for COVID-19. The prevalence of strawberry tongue was calculated. The association with other clinical manifestations of the disease and laboratory findings were studied and the response to treatment was assessed.

Statistical Analysis: Numbers and percentage were used to report categorical variables while mean and standard deviation were given for continuous data, adjusted odd ratio (OR) and 95% confidence interval (CI) were assessed. Students T-test was performed to compare mean of differences between categorical variables. Logistic regression model using chi square test was made to assess the association between this sign and other clinical and laboratory findings. The results were analyzed using SPSS 23 and P value less than 0.05 was considered significant.

Ethical Clearance: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Scientific unit and medical ethics committee of AL-Kindy college of Medicine on April 23rd 2023. Informed consent was obtained from all participants prior to their inclusion in the study.

Participants were informed about the purpose of the study, their right to withdraw at any time without penalty, and the confidentiality of their data. All personal information collected was anonymized to ensure the privacy of the participants.

Results

Patients Characteristics: The study included 50 patients who attended the outpatient internal medicine clinic and tested positive for Covid 19, 64.0% cases were male and 36.0% cases were female. About 40.0% cases were in the age group of 15 to 25 years, 50.0% cases were in the age group of 25 to 35 years and 10.0% cases were more than 35 years’ old (Table 1).

Table 1: Patient Characteristics

Variables	Frequency	Percent
Age Group		
15 to 24 Years	20	40.0
25 to 34 Years	25	50.0
≥ 35 Years	5	10.0
Gender		
Male	32	64.0
Female	18	36.0

Prevalence of Strawberry Tongue: Among the study population, 38(76.0%) patients had sort of “strawberry” tongue. Patients were of younger age group 17(50.0%) patients in the age group of 15 to 25 years, 13 (35.0%) patients in the age group of 25 to 35 years, 8(15.0%) patients aged more than 35 years.

When compared to 50 patients who presented with acute febrile illness (control group) and tested negative for COVID-19, 4(8%) of them had strawberry tongue (Odds ratio 0.1053, 95% CI 0.0350 to 0.3170, P value 0.0001) (Table 2).

Table 2: Provenance of Strawberry Tongue

Group	N(%)	OR(95% CI)	P value
Group I	38(76%)	0.1053(0.035-0.3170)	0.0001
Group II	4(8%)		

Group I= Patients who have strawberry tongue and tested positive for coronavirus; Group II= Patients who have strawberry tongue and tested negative for coronavirus

Clinical Features: The main presenting symptom of all patients was fever (100.0%), fatigue (100.0%) and nausea (100.0%); however, 80.0% of patients with strawberry tongue sign had vomiting and diarrhea (60% cases of the overall population study). About 95.0% of patients with strawberry tongue had hypotension. About 29.0% of patients with strawberry tongue had cough (36.0% of study population). Interestingly, patients who had loss of

the sense of smell and taste did not have strawberry tongue (Table 3).

Table 3: Clinical Features of COVID-19 Positive Patients who had Strawberry Tongue

Symptoms	Total	Case Group	P value
Fever	50(100%)	38(100%)	-
Fatigue	50(100%)	38(100%)	-
Nausea	50(100%)	38(100%)	-
Vomiting	30(60%)	28(80%)	0.04
Diarrhea	30(60%)	28(80%)	0.04
Cough	18(36%)	11(29%)	0.227
Chest pain	5(1%)	2(5.2%)	0.08
Shortness of Breath	2(4%)	1(2.6%)	0.4
Decreased Smell	1(2%)	0(0%)	0.1
Decreased Taste	1(2%)	0(0%)	0.1
HTN	37(74%)	36 (95%)	0.01

Laboratory Findings: About 100.0% of COVID-19 positive patients who had strawberry tongue had high CRP titers, 29.0% of them had elevated liver enzymes (viral hepatitis was excluded), 78.0% had lymphopenia (Table 4).

Table 4: Laboratory Findings of Patients with Covid 19 Positive Patients who Had Strawberry Tongue

Investigation	Total	Case Group	P value
Lymphopenia	43(86%)	30(78%)	0.39
CRP	50(100%)	38(100%)	-
Elevated Liver Enzymes	30(60%)	28(73%)	0.04

Clinical Course: About 78.0% (30 patients) of Covid positive patients strawberry tongue, this sign appeared earlier in the course of the illness (the first two days), 20.0% (7 patients) had this sign within 3 to 4 days of the onset of the symptoms, 2.0% (1 patient) had this sign in the first week. Patients with strawberry tongue had poor response to treatment modalities (acetaminophen, NSAIDS, antibiotics and antiemetic drugs) apart from steroids to which there was excellent response in the form of improved fever, fatigue and Gastrointestinal symptoms so the presence of this sign may be an indirect clue for early initiation of steroid therapy. Patients with strawberry tongue had more prolonged course of illness (20.0% less than one week, 56.0% 1 to 2 weeks, 24.0% more than 2 weeks) in comparison to patients without strawberry tongue (76.0% less than one week) (Table 5).

Tables 5: clinical Course of Illness in Patient Who Have Strawberry Tongue and Tested Positive for Covid-19

Variables	1-2 days	3-4 days	1 st week	2 nd week	> 2 Weeks	OR	95% CI	P value
Time of the first appearance of the sign	30 (78%)	7 (20%)	1 (2%)					
Duration with strawberry tongue			10 (20%)	28 (56%)	12 (24%)	2.333	1.0678-5.0986	0.0001
Duration without strawberry tongue			38 (76%)	10 (20%)	2 (4%)	0.3571	0.01570-0.08122	0.0140

Discussion

Strawberry tongue is a useful clinical sign in various diseases such as Kawasaki disease, Toxic shock syndrome, scarlet fever, and group A streptococcal pharyngitis¹⁸. Red strawberry tongue is an eruption

of the tongue characterized by inflamed and hyperplastic fungiform papillae. In contrast, white strawberry tongue is the presence of a white coating on the tongue through which the hyperplastic fungiform papillae protrude. The white coating represents keratinized epithelium of the filiform

papillae. In patients with red strawberry tongue, the white coating desquamates, and a red and erythematous surface is denuded, interspaced with inflamed and hyperplastic fungiform papillae similar to the seeds of a strawberry¹⁹.

Association of strawberry tongue with covid 19 infection has been recently increasingly reported. M. ramzi described a case with positive COVID-19 IgM, negative IgG and reverse-transcription polymerase chain reaction with Kawasaki disease-like features, her blood investigation revealed lymphopenia, eosinophilia, abnormal liver function, raised C-reactive protein and erythrocyte sedimentation rate with oral steroids, she had an uneventful hospital stay²⁰. A study conducted by Leyla Baykal Selçuk found that 13.9% of patients with multisystem inflammatory syndrome in children had strawberry tongue but it was not significantly associated with the disease severity²¹. It is unclear if COVID-19 causes Kawasaki disease or is a syndrome that mimics Kawasaki disease.

The majority of data was generated from Europe and the US in an online meeting held in early May 2020. A group from the UK recently published a series of 8 children with this multisystem inflammatory syndrome and shortly after, another series of 10 children from Italy was also reported²². The predilection for male gender is similar in classic Kawasaki disease and the Kawasaki disease-like syndrome associated with COVID-19; however, the syndrome associated with COVID-19 appears to affect older children (5 to 14 years) rather than younger children. These patients also have lower white blood cell count, lymphocyte and platelet counts, higher ferritin level, and elevated cardiac markers²².

This study found a significant correlation between gastrointestinal symptoms such as vomiting, diarrhea and the presence of strawberry tongue but minimal respiratory symptoms, these findings were similar to a study done in the united kingdom in which 8 patients presented with fever, conjunctivitis, myalgia and diarrhea and all the patients had fluid refractory shock requiring vasopressors. Surprisingly, there were minimal respiratory symptoms, about 50.0% cases of these patients had a family exposure to SARS-COV-2, but RT-PCR was found to be negative. Majority of patients had some cardiac dysfunction and increased inflammatory markers and troponin²³. There is enough data that suggests the similarity of the symptoms of this infection and Kawasaki disease. However, some differences are also noticed, like age

appears to be higher than the classical Kawasaki disease which is usually 3.

Additionally, these findings have been documented more in African children while Kawasaki is more common in children of Asian ancestry, indicating a racial predisposition. Another striking point is the gastrointestinal symptoms, SARS-COV-2 have the potential to infect enterocytes via ACE2 (angiotensin converting enzyme 2) receptors being expressed in gastric epithelia which can lead to diarrhea in approximately 1/3 infected adults while the occurrence of diarrhea in a post COVID-19 disease is likely not associated directly with infection. In typical Kawasaki disease, emesis is less common than in COVID-19 linked syndrome. The syndrome associated with covid-19 seems to present more gastrointestinal symptoms like vomiting, diarrhea and abdominal pain, compared to classical Kawasaki diseases²⁴. A case published by Boniface Malangu revealed that a patient presented with a Kawasaki-like syndrome with covid 19 positive serology with a prolonged fever of greater than five days in duration along with oral mucosal swelling, bilateral nonpurulent conjunctivitis, a diffuse rash, mild bilateral cervical lymphadenopathy, and evidence of hilar lymphadenopathy. He also had signs of cardiovascular involvement, manifested as new-onset atrial fibrillation, and left ventricular dysfunction.

Similar to the Currently described PIMS-TS or Kawasaki-like disease associated with COVID-19 in children who tested negative for SARS-CoV-2 PCR but have SARS-CoV-2-positive antibodies, this constellation of findings, along with evidence of unregulated inflammatory response and multi-organ failure seen weeks after a viral prodrome, raises the suspicion of a new clinical entity of COVID-19 mimicking Kawasaki disease with the role of steroids, particularly dexamethasone, which has been shown to be an effective treatment for COVID-19, could also be investigated as a potential treatment for adult patients with COVID-19 mimicking Kawasaki disease²⁵.

There are some limitations of the study. The small number of the patients involved in the study. The short duration of the study period. Lack of more advanced research facilities to support the diagnosis like skin biopsy and autoimmune markers.

Conclusion

This study found that a large proportion of patients with fever and positive COVID-19 tests had

strawberry tongue. This sign occurred early in the course of the disease, it is more common in young age group and it is significantly associated with the occurrence of vomiting and diarrhea and it is more associated with a more prolonged fever and good response to systemic steroids. This study found that a large proportion of patients with fever and positive COVID-19 PCR test have strawberry tongue. This sign occurred early in the course of the disease, it is more common in young age group and it is significantly associated with the occurrence of vomiting and diarrhea. It is more associated with a more prolonged fever and good response to systemic steroids. Strawberry tongue sign is commonly found in COVID-19 patients and it might be a useful clinical clue to guide diagnosis and treatment protocol in areas with poor diagnostic facilities; however, more research and studies need to clarify the pathophysiology of this phenomenon and explain the similarities between COVID-19 illness with Kawasaki disease.

Abbreviations

KD: Kawasaki disease

PCR: Polymerase Chain Reaction

Acknowledgments

None

Conflict of Interest

The authors have no relevant conflicts of interest to declare.

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Contribution to authors:

Saman SarKo Baha Al-Den: Conception and design, or design of the research; Sama Atta Gitti: the acquisition, analysis, or interpretation of data; conceptualized and designed the overall study; Saman SarKo Baha Al-Den: involved in data collection; Saman SarKo Baha Al-Den: Drafting the manuscript or revising it critically for important intellectual content; Sama Atta Gitti: involved in data input and data cleaning. Sama Atta Gitti: conducted data analysis; Sama Atta Gitti: drafted the manuscript. Both authors reviewed and approved the final manuscript.

Data Availability

Any questions regarding the availability of the study's supporting data should be addressed to the corresponding author, who can provide it upon justifiable request.

Ethics Approval and Consent to Participate

The Institutional Review Board granted the study ethical approval. Since this was a prospective study, every study participant provided formal informed consent. Each method followed the appropriate rules and regulations.

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