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Clinical Case Report Of Chronic Myeloid Leukemia With A Variant Translocation

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ABSTRACT

Background. In the vast majority of cases, patients with chronic myeloid leukemia (CML) exhibit the classical translocation t(9;22)(q34;q11.2). However, in 5–10% of cases, a chromosomal rearrangement known as a variant translocation is observed, in which additional chromosomes, along with chromosomes 9 and 22, are involved. The prognostic significance of variant translocations remains a controversial issue to date.
Objective. To present a clinical case of chronic myeloid leukemia with a variant translocation t(5;6;9;22)(p15;q26;q22q34;q11.2) and absence of hematological and cytogenetic responses to first-generation tyrosine kinase inhibitor (TKI) therapy.
Materials and Methods. Standard cytogenetic analysis (SCA) of bone marrow and peripheral blood cells from a patient born in 1974 diagnosed with chronic myeloid leukemia.
Results. A variant translocation t(5;6;9;22)(p15;q26;q22q34;q11.2) was identified in this Ph-positive CML patient. Clinical observation revealed the absence of hematological and cytogenetic responses to imatinib therapy, which may be associated with the involvement of additional genetic loci in the pathogenetic translocation.
Conclusion. To draw a definitive conclusion regarding the prognostic value of variant translocations, it is necessary to analyze not only the involved chromosomes and chromosomal loci but also to assess the mutational status of BCR::ABL1, monitor the dynamics of clinical and laboratory parameters, and evaluate the response to TKI therapy.

KEYWORDS: chronic myeloid leukemia, cytogenetic analysis, chromosomal abnormalities, variant translocations

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INTRODUCTION

Among malignant hematological disorders in humans, chronic myeloid leukemia (CML) is one of the most thoroughly studied neoplasms [1,2]. A breakthrough in understanding the biology of this leukemia was the discovery of the Philadelphia (Ph) chromosome in 1960. It was later determined that the Ph chromosome is the result of a reciprocal chromosomal translocation t(9;22), involving the ABL1 and BCR genes, located on chromosomes 9 and 22, respectively. This rearrangement results in the formation of the BCR:ABL1 oncogene, which encodes a chimeric protein with constitutively high tyrosine kinase activity [3,4]. This leads to uncontrolled proliferation of myeloid cells, reduced apoptosis and adhesion, causing marked myeloid hyperplasia in the bone marrow and the release of immature myeloid cells into the peripheral blood [5,6].

In the majority of cases, cytogenetic analysis of leukemic cells in CML patients reveals the classical translocation t(9;22)(q34;q11.2). However, in 5–10% of patients, one or more additional chromosomes may be involved in the pathogenetic rearrangement alongside chromosomes 9 and 22. These chromosomal abnormalities, known as variant translocations, are of particular interest due to conflicting data regarding their relevance to treatment response, including to tyrosine kinase inhibitors (TKIs), as well as to survival prognosis across different patient groups [7,8].

PURPOSE OF THE RESEARCH

The aim of this study is to present a clinical case of chronic myeloid leukemia with a variant translocation t(5;6;9;22)(p15;q26;q22q34;q11.2) and an absence of hematological and cytogenetic responses to first-generation tyrosine kinase inhibitor (TKI) therapy.

MATERIALS AND METHODS

The subject of the study was a male patient, S.N., born in 1974, diagnosed with chronic myeloid leukemia and observed at the Republican Specialized Scientific and Practical Medical Center of Hematology (RSSPMCH) under the Ministry of Health of the Republic of Uzbekistan since 2017.

Analysis of blood cell elements was performed using the hematology analyzer "SYSMEX. GLOBAL IMPEX" (Japan) with reagents from "HUMAN" (Germany), and also via manual microscopy (microscope: LEICA ICC50 E, Germany), equipped with a 5-megapixel color digital camera (2592 × 1944). The erythrocyte sedimentation rate (ESR) was determined using the Panchenkov apparatus (Russia).

The cellular composition of the bone marrow aspirate was analyzed by manual microscopy (LEICA ICC50 E, Germany) with the same 5-megapixel digital color camera.

For standard cytogenetic analysis (SCA), 24-hour cultures of bone marrow and peripheral blood cells were used. Stabilization and preparation of metaphase spreads, as well as staining of cytogenetic slides, were performed using standard protocols. Metaphase plate screening and analysis were conducted at magnifications of ×200 and ×1000 (microscope: AXIO Scope.A1, Zeiss, Germany). Karyotype analysis was performed using the "VideoTest-Karyo 3.1" software (Russia). Chromosome identification followed the International System for Human Cytogenomic Nomenclature (ISCN) [9].

RESULTS

Clinical Observation

Subjectively, patient S.N., born in 1974, began experiencing malaise in March 2017. As his general condition deteriorated—with increasing fatigue, weight loss, tinnitus, shortness of breath upon minimal physical exertion, palpitations, decreased appetite, abdominal bloating, pain and heaviness in the left hypochondrium, bone pain, and fever—he sought medical attention at the Kashkadarya Regional Multidisciplinary Medical Center (KRMMC, Karshi, Uzbekistan), from where he was referred to the Samarkand Regional Multidisciplinary Medical Center (SRMMC, Samarkand, Uzbekistan).

Upon examination at the SRMMC on September 26, 2017, the patient's general condition was assessed as relatively severe. This was due to tumor proliferation syndrome, tumor intoxication, and anemia. Notably, hepatomegaly (+2 cm) and splenomegaly (+13 cm) were observed. No enlargement of peripheral lymph nodes was found. The results of the complete blood count and bone marrow smear dated September 27, 2017, are presented in Table 1.

Table 1
Results of Complete Blood Count and Bone Marrow Findings Over Time

Date, Location, and Treatment Stage	Complete Blood Count	Myelogram
27.09.2017 SRMMC Diagnosis	Hemoglobin – 50.0 g/L; Erythrocytes – 2.6×10^{12}/L; Platelets – 1173×10^{9}/L; Leukocytes – 407.4×10^{9}/L; Blasts – 9%; Promyelocytes – 13%; Myelocytes – 6%; Band neutrophils – 20%; Segmented neutrophils – 32%; Basophils – 9%; Eosinophils – 5%; Monocytes – 6%; ESR – 19 mm/h	Bone marrow aspirate: adequately cellular; maturation arrest at the myelocyte stage; hematopoiesis type – normoblastic; erythroid lineage suppressed; blasts – 6.4%; myeloid-to-erythroid ratio – 12.8:1
06.10.2017 SRMMC After 10-day hydroxyurea therapy	Hemoglobin – 82.0 g/L; Erythrocytes – 2.9×10^{12}/L; Platelets – 1583×10^{9}/L; Leukocytes – 42.0×10^{9}/L; Blasts – 0%; Promyelocytes – 0%; Myelocytes – 4%; Band neutrophils – 21%; Segmented neutrophils – 51%; Basophils – 6%; Eosinophils – 2%; Monocytes – 6%; Lymphocytes – 10%; ESR – 19 mm/h	–
11.10.2017 RSSPMCH After 10-day hydroxyurea therapy	Hemoglobin – 82.0 g/L; Erythrocytes – 3.0×10^{12}/L; Platelets – 180.0×10^{9}/L; Leukocytes – 14.4×10^{9}/L; Blasts – 0%; Promyelocytes – 2%; Myelocytes – 3%; Metamyelocytes – 5%; Band neutrophils – 2%; Segmented neutrophils – 65%; Basophils – 0%; Eosinophils – 0%; Monocytes – 3%; Lymphocytes – 20%; ESR – 5 mm/h	Bone marrow aspirate: hypercellular; granulocytic lineage unchanged; hematopoiesis type – normoblastic; erythroid lineage – within normal range; adequate megakaryocytes; platelet clusters present. Blasts – 1.8%; Promyelocytes – 3.6%; Myelocytes – 11.4%; Metamyelocytes – 14.2%; Band neutrophils – 16.0%; Segmented neutrophils – 24.2%; Eosinophils (all stages) – 0.8%; Basophils – 2.8%; Monocytes – 2.0%; Lymphocytes – 9.0%; Plasma cells – 0.8%;

		Erythroblasts – 0.2%; Pronormoblasts – 2.0%; Basophilic normoblasts – 2.4%; Polychromatic normoblasts – 6.8%; Oxyphilic normoblasts – 2.0%; Myeloid-to-erythroid ratio – 6.46:1; Erythrocyte maturation index – 0.65; Bone marrow neutrophil index – 0.77
13.09.2018 RSSPMCH After 10 months and 4 days of imatinib therapy (400 mg/day)	Hemoglobin – 68.0 g/L; Erythrocytes – 2.0×10^{12}/L; Platelets – 18.0×10^{9}/L; Leukocytes – 2.3×10^{9}/L; Band neutrophils – 2%; Segmented neutrophils – 40%; Basophils – 1%; Lymphocytes – 57%; ESR – 60 mm/h	Bone marrow aspirate: hypocellular; Lymphocytes – 14%; erythroid lineage not suppressed; no megakaryocytes observed
21.09.2018 RSSPMCH After dexamethasone (N8), trombonorm (N7), RBC transfusions (N2), imatinib discontinued	Hemoglobin – 106.0 g/L; Erythrocytes – 2.61×10^{12}/L; Platelets – 20.8×10^{9}/L; Leukocytes – 4.6×10^{9}/L; Segmented neutrophils – 55%; Monocytes – 9%; Lymphocytes – 36%; ESR – 70 mm/h	–
11.03.2020 RSSPMCH Resumption of imatinib therapy (400 mg/day), duration since resumption: 16 months and 28 days	Hemoglobin – 99.0 g/L; Erythrocytes – 3.31×10^{12}/L; Platelets – 1131×10^{9}/L; Leukocytes – 396.65×10^{9}/L; Band neutrophils – 31.9%; Segmented neutrophils – 76.5%; Eosinophils – 11.61%; Lymphocytes – 5.4%	Bone marrow aspirate: hypercellular; granulocytic lineage hyperactive; Lymphocytes – 1%; erythroid lineage suppressed; Megakaryocytes – 15%; local platelet clusters present
24.03.2020 RSSPMCH After 10-day hydroxyurea therapy with continued imatinib 400 mg/day	Hemoglobin – 87.0 g/L; Erythrocytes – 3.38×10^{12}/L; Platelets – 708.0×10^{9}/L; Leukocytes – 7.13×10^{9}/L; Segmented neutrophils – 42.9%; Monocytes – 2%; Lymphocytes – 33.9%; Basophils – 19.4%; ESR – 25 mm/h	–
10.03.2021 KRMMC Continued imatinib therapy (400 mg/day), total duration: 28 months and 27 days	Hemoglobin – 131.0 g/L; Erythrocytes – 4.7×10^{12}/L; Platelets – 504.0×10^{9}/L; Leukocytes – 23.02×10^{9}/L; Segmented neutrophils – 71.7%; Monocytes – 5.3%; Lymphocytes – 16.6%; Eosinophils – 0.6%; Basophils – 5.8%; ESR – 5 mm/h	–

Based on clinical and laboratory findings, the patient was diagnosed with chronic myeloid leukemia (CML), and the following treatment was initiated: hydroxyurea (1000 mg/day, treatment duration – 10 days), allopurinol (300 mg/day), and transfusion of red blood cell concentrate No. 2 (0 αβ (I) Rh+). The results of the complete blood count performed at SRMMC on October 6, 2017, after the administered therapy are presented in Table 1.

For further diagnostic evaluation, the patient was referred to the RSSPMCH. The results of the complete blood count and bone marrow aspiration performed at RSSPMCH on October 11, 2017, are presented in Table 1. Standard cytogenetic analysis conducted on October 11, 2017, revealed a characteristic derivative of chromosome 22 (Philadelphia chromosome), which is the cytogenetic manifestation of t(9;22)(q34;q11.2) in leukemic cells. However, analysis of the second component of the pathogenic translocation—the derivative of chromosome 9—as well as verification of the presence or absence of additional chromosomal abnormalities was not possible due to the poor quality of the metaphase spreads (indistinct morphology and absence of G-banding). Due to technical limitations, molecular genetic testing for the BCR::ABL1 (p210) transcript was not performed.

Based on clinical and laboratory data and the results of standard cytogenetic analysis, the diagnosis of chronic myeloid leukemia was confirmed, and the patient was prescribed therapy with imatinib (NOVARTIS) at a dose of 400 mg/day, which he reportedly took regularly starting from November 8, 2017, for 10 months under complete blood count monitoring. The patient declined further monitoring of treatment response using standard cytogenetic and molecular genetic methods due to the logistical difficulty of traveling to RSSPMCH from a remote region.

Due to deterioration in his general condition, on September 13, 2018, the patient was hospitalized in the hematology department of RSSPMCH. Upon admission, his general condition was assessed as severe, primarily due to the presence of anemic syndrome.

The skin and visible mucous membranes were clean and pale pink; the tongue was moist. Heart sounds were muffled; pulse was regular at 82 beats per minute; blood pressure was 120/70 mmHg. No enlargement of peripheral lymph nodes was noted. Nasal breathing was unlabored; auscultation revealed vesicular breathing. The abdomen was soft and non-tender. The liver and spleen were palpated at the costal margin. Stool and urination were unremarkable. The results of the complete blood count and bone marrow aspiration performed at RSSPMCH on September 13, 2018, are shown in Table 1.

Clinical and laboratory data indicated the development of myelotoxic agranulocytosis associated with imatinib therapy. The severity of treatment-related adverse events, according to CTCAE version 5.0, was assessed as follows: grade 3 anemia, grade 3 neutropenia, and grade 4 thrombocytopenia. Due to hematologic toxicity, imatinib therapy was temporarily discontinued. The patient received supportive therapy, including dexamethasone (12 mg/day IV for 8 days), tranexamic acid (5.0 mL IV for 7 days), and transfusion of red blood cell concentrate No. 2 (0 αβ (I) Rh+). The blood parameters following this inpatient treatment, dated September 21, 2018, are presented in Table 1.

After recovery of absolute neutrophil count to above 1.0×10⁹/L and platelet count to above 50×10⁹/L (on October 20, 2018), the patient resumed imatinib therapy at a dose of 400 mg/day. According to the patient, the TKI was taken regularly for 16 months and 28 days. However, due to a decline in general health status, he was re-hospitalized in the hematology department of RSSPMCH on March 11, 2020. Upon admission, the patient was conscious but his overall condition was again assessed as severe, due to tumor intoxication syndrome. An increase in spleen size (+5 cm) was noted, while the liver remained at the costal margin. The results of the complete blood count and bone marrow aspiration performed at RSSPMCH on March 11, 2020, are presented in Table 1.

Repeat standard cytogenetic analysis of leukemic cells, performed on March 17, 2020, revealed a variant translocation t(5;6;9;22)(p15;q26;q22q34;q11.2) in 100% of the analyzed metaphase spreads (22 out of 22) (Figure 1).

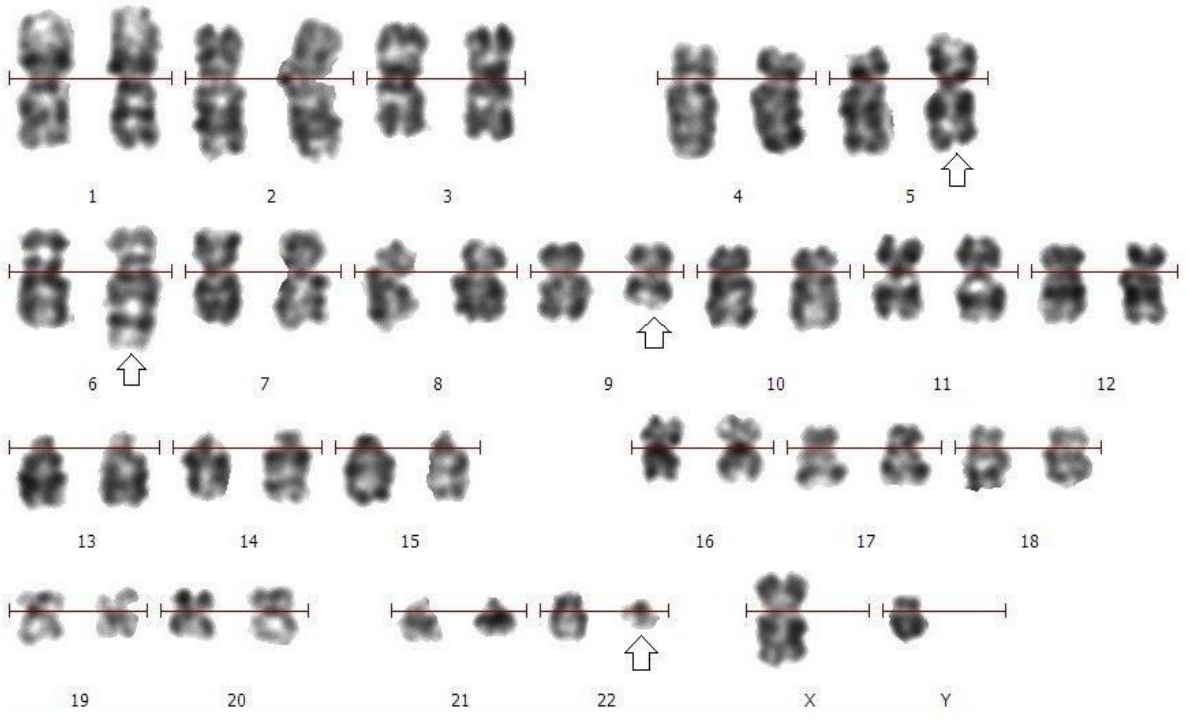

Figure 1. Karyogram of leukemic cells from patient S.N. (VideoTestKaryo 3.1). Arrows indicate the derivative chromosomes 5, 6, 9, and 22 involved in the variant translocation t(5;6;9;22)(p15;q26;q22q34;q11.2).G-banding. Magnification ×1000.

The patient's TKI therapy was temporarily discontinued, and treatment was initiated with hydroxyurea (4000 mg/day), allopurinol (300 mg/day), and symptomatic therapy. After treatment at RSSPMCH, the leukocyte count decreased (CBC of 24.03.2020; see Table 1), the patient's condition stabilized, and he was discharged with recommendations to continue imatinib at 400 mg/day under monitoring by a hematologist at his place of residence.

The patient refused molecular-genetic testing of BCR::ABL1 (p210) due to the logistical difficulty of traveling to RSSPMCH. On a follow-up blood test 12 months later (10.03.2021; Table 1), thrombocytosis exceeding 500×10⁹/L and leukocytosis exceeding 20×10⁹/L were observed. In March 2021, the patient died.

DISCUSSION

Based on the clinical and laboratory data and the results of cytogenetic testing, the diagnosis of chronic myeloid leukemia was confirmed. The rationale for initiating TKI therapy was the cytogenetic analysis using standard cytogenetic methods, which due

to the suboptimal quality of metaphase spreads allowed only the detection of the marker Ph chromosome. This precluded determination of whether the pathogenic translocation was classical or variant, the involvement of additional chromosomes or chromosomal loci, and differentiation of variant translocations from additional clonal chromosomal aberrations. The latter point is especially important because, while the prognostic significance of variant translocations remains ambiguous, the detection of additional clonal chromosomal aberrations (ACAs) indicates a higher probability of disease progression and complicates treatment [10,11].

Upon repeat standard cytogenetic analysis (SCA), in 100% of the assessed metaphase spreads from this CML patient—diagnosed based on clinical data and the previously detected Ph chromosome—not only the derivative chromosome 22 (Ph chromosome) but also the atypically altered chromosome 9 and derivatives of chromosomes 5 and 6 were identified (Figure 1).

G-banding analysis showed that the chromatin breaks, besides at loci 9q34 and 22q11.2, also occurred at 9q22, 5p15, and 6q26. As a result of this rearrangement: the 9q22–terminal fragment (carrying a portion of 22q11.2–terminal) became joined to the terminus of the long arm of chromosome 6 (locus 6q26); the 6q26–terminal fragment attached to the short arm of chromosome 5 (locus 5p15); and the 5p15–terminal fragment joined to the terminal region of the long arm of the derivative chromosome 9 (locus 9q22). Thus, structural modeling indicates that despite breaks in four chromosomes, the karyotype cannot be classified as complex. Complex karyotypes—which, like +8, a second Ph chromosome, i(17q), +19, –7/7q–, or structural rearrangements involving 3q26.2 and 11q23—are known prognostic markers of disease progression and poor TKI response [12]. In this case, the rearrangements involving chromosomes 5 and 6 appear not to be secondary clonal aberrations but integral parts of the variant translocation t(5;6;9;22)(p15;q26;q22q34;q11.2).

Tracking disease dynamics and response to imatinib (400 mg/day) since 2017 shows episodes of myelotoxic agranulocytosis (13.09.2018; Table 1). Meanwhile, during ongoing TKI therapy (11.03.2020; Table 1), the platelet count rose to 1,131×10⁹/L and leukocyte count to 396.65×10⁹/L; after administration of hydroxyurea, levels declined to 708.0×10⁹/L and 7.13×10⁹/L, respectively (24.03.2020; Table 1). Moreover, the detection of the Ph chromosome (derivative 22) in 100% of leukemic cells at repeat karyotyping—more than two years into therapy—suggests absence of a cytogenetic response to TKI.

Assessment by the Sokal score before therapy placed the patient in a high-risk group (index = 2.3) with an estimated 2-year survival of 65% and median survival of 2.5 years. The patient also scored high risk by EUTOS (115 points) and ELTS (2.438 points).

Changing the treatment plan temporarily stabilized his condition; however, the high-risk classification by Sokal, EUTOS, and ELTS, absence of hematologic and cytogenetic response to imatinib, and the patient's death three and a half years after diagnosis indicate a poor disease course. The poor outcome might have been related to one of the BCR::ABL1 kinase-domain mutations conferring imatinib resistance; however, due to lack of access to mutation screening, this analysis was not done. Nonetheless, one cannot rule out a possible relationship between the absence of cytogenetic response and the presence of t(5;6;9;22)(p15;q26;q22q34;q11.2) discovered on repeat karyotyping. Variant translocations are usually identified at initial SCA—only when metaphase spreads have clear morphology and distinguishable G-banding, allowing structure identification and full karyotype evaluation.

Most investigators maintain that variant translocations do not influence cytogenetic or molecular response or outcome, regardless of whether their formation is one- or multi-step, the number of chromosomes involved, or the presence of deletions in der(9) [4,7,13]. ELN recommendations also lack a "warning" for patients with variant translocations. However, the literature offers limited data suggesting that the prognostic value of variant translocations remains unresolved and requires further elucidation [14]. For example, W. Al-Achkar et al. (2013) reported a CML case with variant translocation t(9;10;22)(q34;p11.2;q11) and Y chromosome loss, resistant to imatinib [15]. S. Aliano et al. (2013) described a CML patient with two cytogenetic clones: an imatinib-sensitive clone with classic t(9;22) and an imatinib-resistant clone with translocation t(9;11;22)(q34;p15;q11) and E255V / E258V mutations in the BCR::ABL1 kinase domain [16]. In a study by M. El-Zimaity et al. (2004) of 721 CML patients, variant translocations were found in 44; they observed that patients with variant translocations more frequently entered accelerated phase than those with t(9;22), but no significant effect of variant translocation on response rate or overall survival was established [17].

The variant translocation we identified involved breaks in at least five loci (5p15, 6q26, 9q22, 9q34, and 22q11.2), which may occur by chance but also suggests genomic instability of the leukemic clone and presence of cryptic rearrangements. Although variant translocations are considered prognostically neutral under certain views, involvement of additional chromosomal loci may lead to genetic changes that contribute independently to the leukemic clone's tumor phenotype and clinical course.

CONCLUSION

The prognostic significance of variant translocations in CML remains a controversial issue. The presented high-risk patient case, featuring a pathogenic rearrangement involving chromosomes 5, 6, 9, and 22, demonstrates absence of hematologic and cytogenetic responses to imatinib, possibly indicating an unfavorable prognostic role for t(5;6;9;22)(p15;q26;q22q34;q11.2). At the same time, definitive conclusions about the prognostic significance of variant translocations require accumulation of further cases with mandatory identification of involved chromosomes and loci, assessment of the BCR::ABL1 kinase-domain mutational status, tracking of clinical-laboratory dynamics, and responses to TKI therapy. Differentiating a variant translocation involving chromosomes 9 and 22 from complex karyotypic abnormalities due to additional chromosomal aberrations is feasible via standard karyotyping—but only if high-quality metaphase spreads allow morphological and banding analysis in accordance with the

International System for Human Cytogenomic Nomenclature.

Conflicts of interest
The authors declare no conflicts of interest.

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