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Possible Reye's syndrome following respiratory syncytial virus infection in a child without Aspirin exposure: A case report

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Case Report

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Abstract

We present a case report of an association between a possible case of Reye's syndrome and respiratory syncytial virus (RSV) in the absence of aspirin use. Although Reye's syndrome has been reported after certain viruses, such as influenza A and B, and the use of aspirin during the period of infection is a known cause of this syndrome, its occurrence after respiratory syncytial virus in a healthy child without risk factors is rare. Our case involves an 8-year-old girl who presented with flu-like symptoms, nausea, respiratory distress, and confusion. Laboratory tests indicated a significant increase in liver enzymes and tested positive for RSV. Further investigation ruled out other possible diagnoses, and Reye's syndrome was placed as the primary diagnosis. This case points to the fact that although the incidence of Reye's syndrome has decreased over the years and there are known etiologies for it, considering the speed of the disease's progression and the mortality rate, it should be considered in children who have evidences of Reye's syndrome and appropriate investigations should be carried out.

Introduction

Respiratory syncytial virus (RSV) is one of the most prevalent etiologies of lower respiratory tract infections among infants and young children, causing a large number of pediatric clinic visits (1). RSV infection can cause various symptoms ranging from colds to severe pneumonia and bronchiolitis requiring hospitalization (2, 3), and it is responsible for about 100000 deaths among young children, especially in low and middle-income countries (4). It has been proven that in pediatrics, having an underlying disease is a risk factor for developing a more severe RSV infection (5). The disease is no longer considered a serious threat only to children under 2 years old, but it has evolved into a condition that can affect people of all ages (6). There are evidences that show RSV disease can be more severe and deadly than COVID-19 and Influenza, and patients hospitalized due to RSV disease are more likely to need supplemental oxygen and ICU care (7).

Reye's syndrome is a rare but serious condition presenting with non-inflammatory encephalopathy and fatty liver failure, mostly associated with viral infections such as Influenza A and B and Varicella (8). It seems that Reye's syndrome occurs due to mitochondrial dysfunction, which, in liver cells, causes an increase in ammonia levels. This leads to cerebral edema and a rise in intracranial pressure (ICP) (8, 9).

Aspirin intake during viral infections is known to be a triggering factor for Reye's syndrome in young children (10).

To our knowledge, Reye syndrome following respiratory syncytial virus infection in the absence of aspirin exposure has rarely been reported in the literature. Although the occurrence of Reye's syndrome is less common in RSV infection, the combination of respiratory distress, liver failure, and neurological deterioration is clinically important and requires careful investigation.

De-identification

All patient information in this presentation has been de-identified to maintain confidentiality and protect patient privacy.

Case presentation

An 8-year-old girl with a history of heart surgery for patent ductus arteriosus (PDA) was referred from another clinic to our hospital due to vomiting, respiratory distress, and an elevation in liver enzymes. She had a history of flu-like symptoms, including fever, cough, and throat irritation that began 5 days before her admission. She was treated with Ceftriaxone for the initial diagnosis of pneumonia, but her respiratory distress worsened, and on further investigation, there was an elevation in AST and ALT levels. Because of the concern about her condition, she was referred to our hospital.

The child presented with altered mental status, sleepiness, and confusion. She was hemodynamically unstable and her vital signs were concerning at the time of admission: She had a fever of 39°C, blood pressure of 90/60 mmHg, pulse rate 150 per minute, respiratory rate 60 breaths per minute, and oxygen saturation (SpO2) at 60%. On physical examination, diffuse wheezing and crackles on lung auscultation were noted, capillary refill time (CRT) was within normal range and under 2 seconds, and urinary output was maintained. We observed facial anomalies, including malformed and low-set ears.

She was the second child, and her parents were related. Past drug history was obtained from the patient's parents, and it was noted that she only used acetaminophen for fever management. She did not take aspirin or any other NSAIDs for her fever.

The patient was transferred to the intensive care unit (ICU) for further care. We treated the patient with bilevel positive airway pressure (BiPAP) and this led to a marked improvement in his oxygen saturation, which rose to 94%. Given the patient’s condition we empirically initiated antibiotic therapy with Vancomycin, Cefotaxime, Metronidazole and Azithromycin. This broad-spectrum approach was aimed at covering a wide range of potential pathogens.

Laboratory tests, including complete blood count (CBC), liver function tests, renal function assessment, and venous blood gas (VBG), were ordered to monitor the patient's overall condition. There was a significant elevation in AST and ALT levels, with AST measuring 3696U/L and ALT at 2944U/L, prothrombin time (PT) was elevated at 25 seconds. Albumin levels were found to be low at 3.5g/dl, and bilirubin levels were within the normal range. Ammonia levels were also elevated at 85µg/dL. We initiated lactulose due to the high ammonia level.

Other laboratory tests are listed in the table below, along with their progression as we started the treatment (Table-1).

Table 1
laboratory results and their progression after starting treatment and during follow-up

WBC	**First day of hospitalization**	**The seventh day of hospitalization**	**Five days after discharge**	**Normal range**
	13600	**9100**	**8100**	**5000–13000 Cells/μL**
RBC	4.84	5.53	5.7	4-5.2 Mil/μL
Hb	8.8	11	10.9	11.5–15.5 g/dL
Platelets	106000	150000	329000	170000–450000 K/μL
Neutrophils	54.2	40	45	35–65%
Lymphocytes	38.5	53	50	23–53%
Blood sugar	120	85	82	70–135 mg/dL
BUN	12	13	12	7-16.8 mg/dL
Creatinine	0.6	0.64	0.61	0.5–0.83 mg/dL
AST	3696	41	34	10–51 U/L
ALT	2944	191	44	10–39 U/L
ALP	252	285	274	100–720 U/L
Bilirubin (Total)	0.3	0.6	0.5	0.1–1.1 mg/dL
Bilirubin (Direct)	0.1	0.2	0.2	0.1–0.3 mg/dL
Albumin	3.3	4.2	4.5	3.80–5.40 g/dL
Calcium	7.9	9.6	9.8	8.8–10.8 mg/dL

WBC	First day of hospitalization	The seventh day of hospitalization	Five days after discharge	Normal range
	13600	**9100**	**8100**	**5000–13000 Cells/μL**
Ammonia	80	45	27	11–54 μg/dL
APTT	28	32	28	25–38 Seconds
PT	25.1	13.9	12.7	12–14 Seconds
INR	2.09	1.05	1.06	1-1.20
Fibrinogen	131	170	220	200–400 mg/dL
Ferritin	1650	221	97	7–84 ng/dL
CRP	5	3	2	1–7 mg/L
ESR	3	4	2	0–10 mm/h
V_pH	7.327	7.437	7.54	7.35–7.43
V_pCO2	45.2	43	36.1	32–46 mmHg
V_HCO3	23	28.6	30.8	21–26 mmol/L
Troponin	0.66	0.16		0-0.02 ng/mL
Pro-calcitonin	0.26			PCT > 2.0 ng/mL= positive PCT < 0.05 ng/mL= positive

Due to her respiratory distress and altered mental status, we also requested a chest X-ray and a brain CT scan.

Chest x ray revealed bilateral infiltrates. The presence of widespread lung involvement suggested possible viral etiology (Figure-1). And on the brain CT scan, we observed cerebral edema (Fig. 2).

Because of the concern for a potential viral or bacterial co-infection, a sepsis pathogen panel and respiratory multiplex PCR that included COVID-19 and influenza, was requested to identify any probable pathogens. Blood cultures were also obtained to assess bacteremia, along with the Legionella urine antigen and PCR, Coxiella Brunetti (Q fever) IgG and IgM, Bartonella IgG and IgM and Rickettsia Conorii IgG and IgM, which all came back negative. Of all the requested tests, only the PCR for respiratory syncytial virus was positive.

We also requested rheumatological and immunological factor tests, including nitro-blue tetrazolium blood test (NBT), antimitochondrial antibodies (AMAs), anti-smooth muscle antibody (ASMA), anti-liver-kidney microsome antibodies (anti-LKM), CH50, C3, and C4, which were negative. In addition to the negative COVID PCR, an anti-spike antibody test was requested to rule out the possibility of multisystem inflammatory syndrome (MIS-C), and it was reported as negative.

As we mentioned before, we noticed facial anomalies in patient's face, including malformed and low-set ears, therefore we proceeded with a karyotype analysis and a fluorescence in situ hybridization (FISH) test to assess for 22q11.2 deletion syndrome, and because of the fact that some inborn errors of metabolism (IEM) disorders can present with Reye-like-syndrome, we tested the patient for possible probabilities such as amino acid analysis by HPLC, urine organic acid analysis and plasma lactate test, which they were negative.

Given that the child's condition was initially unstable, it was not possible to perform an lumbar puncture (LP) or liver biopsy but due to the rapid progression of the patient's symptoms. Hepatic encephalopathy and evidences of cerebral edema on her brain CT-scan, threefold elevation of serum transaminases and serum ammonia without an increase in bilirubin, coagulation abnormalities and a recent viral infection, along with the exclusion of other potential causes, Reye's syndrome was proposed as a possible diagnosis.

On her first day of admission, the patient developed a mild maculopapular rash, which became more diffuse during her hospitalization, spreading to her arms, legs, face, and even the palms of her hands. The rash included both maculopapular and petechial components (Fig. 3). As the rash worsened, a biopsy was performed. The results showed a vasculopathic reaction pattern.

During the admission, there was a mild elevation in troponin level at 0.6ng/ml. electrocardiogram (ECG) showed a normal sinus rhythm with ST depression and inverted T waves in pre-cordial leads. These findings strongly suggested myocarditis as a complication of recent viral infection. We treated the patient with intravenous immunoglobulin (IVIG) (Fig. 4).

After a few days she showed significant improvement, initially her level of consciousness got better, followed by a reduction in respiratory distress. She was gradually weaned off the BIPAP and finally she no longer required oxygen support. There was a noticeable improvement in her liver enzymes, coagulation factors, and other key laboratory test results as shown in the table above. After continuing treatment, the rashes also began to improve.

Discussion

In the present study, we discussed the case of an 8-year-old girl who developed respiratory distress and hepatic encephalopathy after contracting RSV. After ruling out other possible diagnoses, Reye's syndrome was considered the most likely diagnosis.

RSV is the leading cause of pulmonary involvement in children (1, 3) and it is known that younger children and children with an underlying diseases are at risk of developing serious infection after RSV (11), but recent studies suggest that the association between age and RSV has changed during the post-covid era (12), it is because of the fact that levels of RSV-specific antibodies have declined, with a more significant decrease observed in older children (5). During the post-COVID era, due to the immunity debt, viruses such as RSV and influenza erupted, and in addition to off-season outbreaks, their severity has also increased (5, 12). Reye syndrome is a rare but potentially fatal illness that affects children, usually between the ages of 5 and 14 (8). The incidence of this syndrome has been greatly reduced due to the warning about not using aspirin in children under 12 years of age (8, 10). Although Reye syndrome has occurred more often after being infected with viruses such as influenza A and B (5), and according to our research, no case of Reye syndrome has been seen after RSV, our patient fulfilled the clinical criteria for Reye syndrome.

Given the well-established association between Reye syndrome and influenza viruses in the context of salicylate exposure, the occurrence of Reye-like illness following RSV infection without aspirin use appears to be distinctly uncommon and merits clinical attention. Considering the rapid course of Reye syndrome and its mortality rate, early diagnosis is necessary. It is also important to note that, given that RSV appears to have reemerged in recent years, clinicians should pay close attention to this virus and the complications it may cause.

Conclusion

The incidence of Reye syndrome has decreased over the years but our patient had classic manifestations of hepatic encephalopathy, which could not be explained by any other differentials. It is necessary to consider other triggers such as RSV for this syndrome in addition to known viral etiologies and Aspirin use, and more researches should be done in this field.

Declarations

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (approval Code: IR.ARI.MUI.REC.1404.168). All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the principles of the Declaration. Written informed consent was obtained from the patient's parents to use her information

and medical records to conduct this case report study, including any accompanying images and clinical data.

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Declaration of Competing Interests / Conflicts of Interest:

The authors declare that they have no competing interests. The authors confirm that there are no financial or non-financial conflicts of interest that could have influenced the work reported in this manuscript.

Author Contribution

• Rana Saleh contributed to conceptualization, data curation, editing, and supervision.• Amir Hossein Ghandehari contributed to writing the original draft.• Zahra Pourmoghaddas contributed to editing and supervision.• Arezoo Khalili Borujeni contributed to data curation, writing the original draft, and editing.All authors read and approved the final manuscript.

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Figures

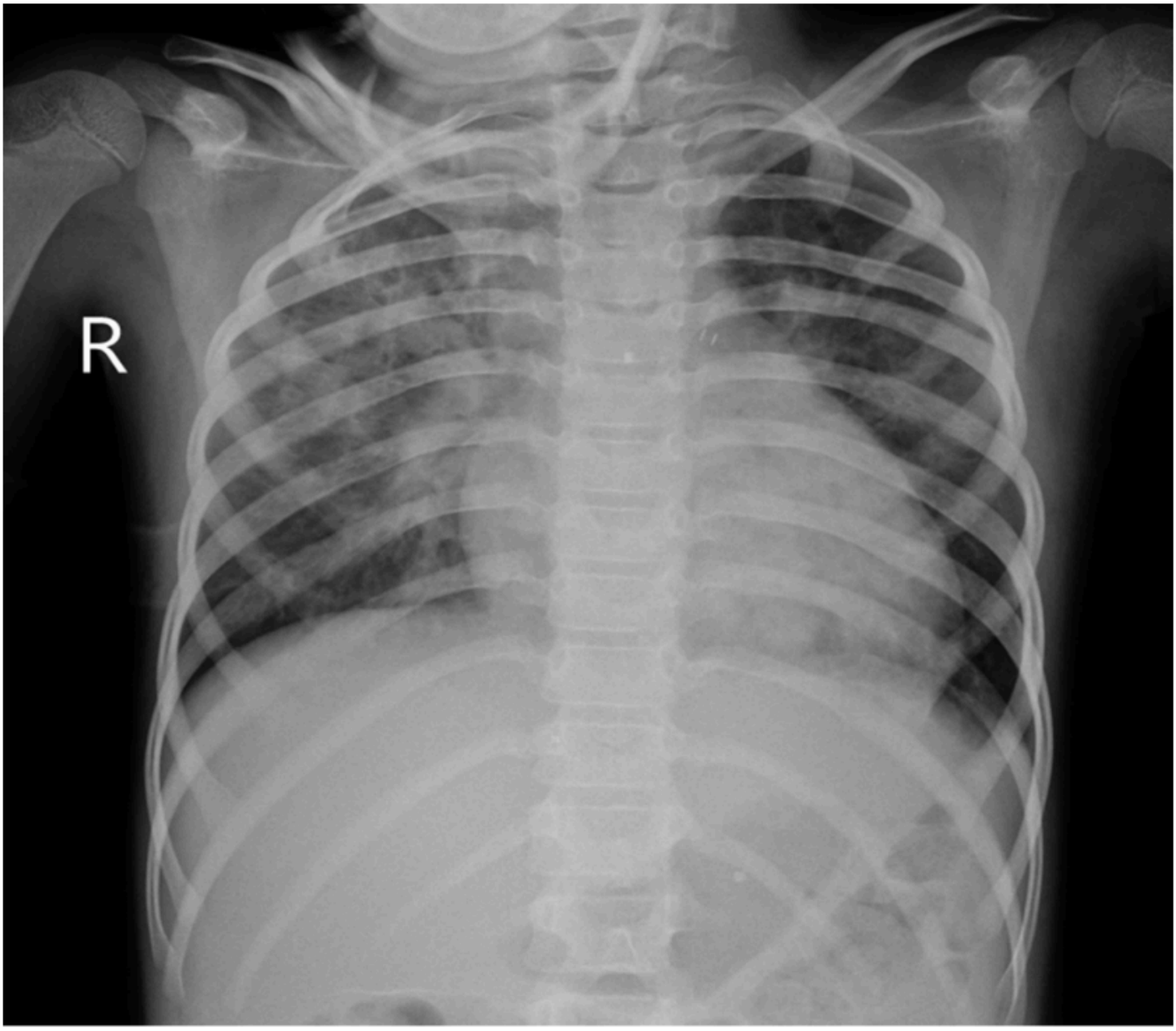


Figure 1: PA chest x-ray

Figure 1

See image above for figure legend.

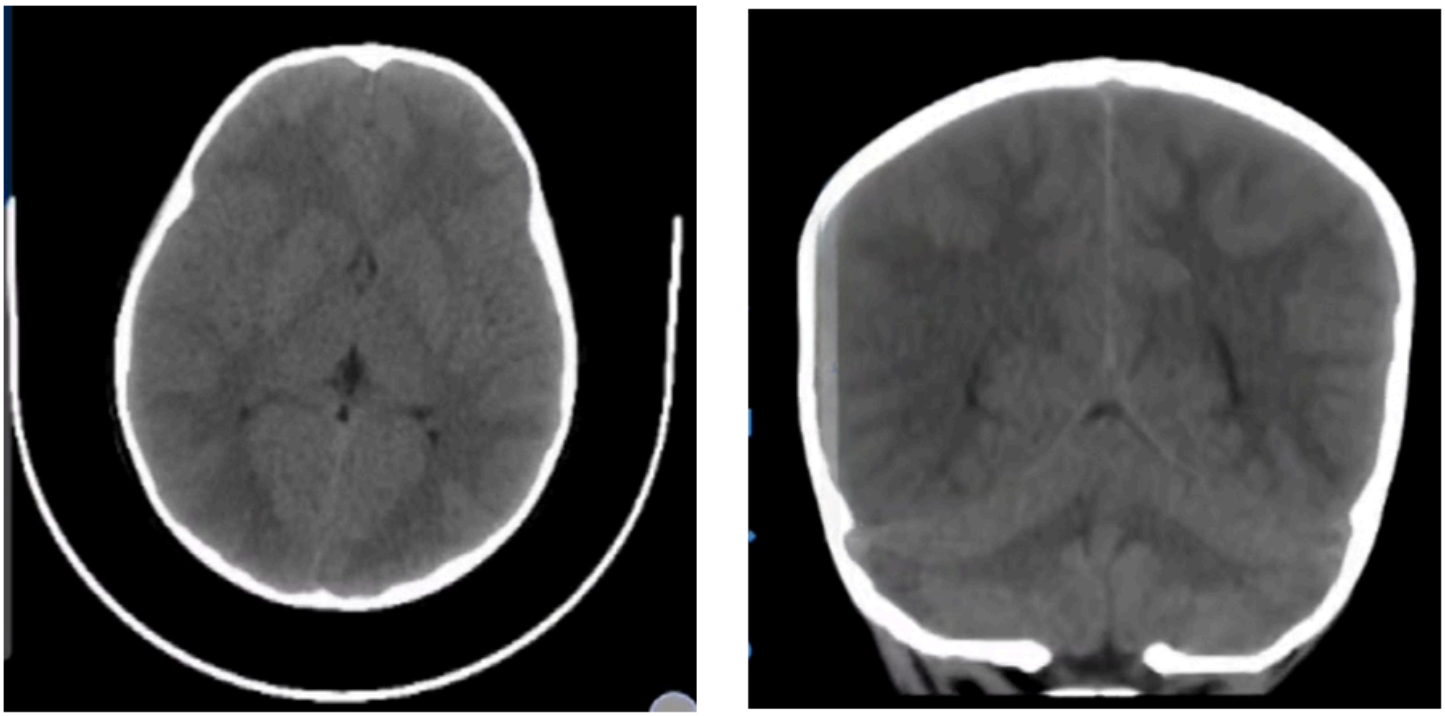


Figure 2: Brain edema on CT-scan

Figure 2

See image above for figure legend.

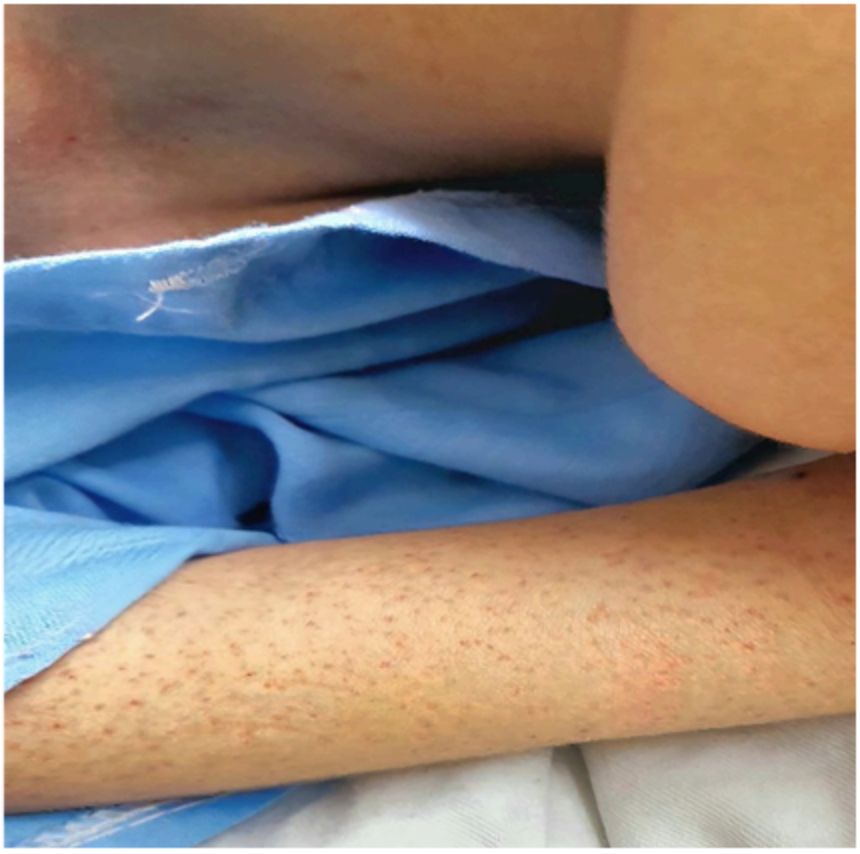


Figure 3

Figure 3

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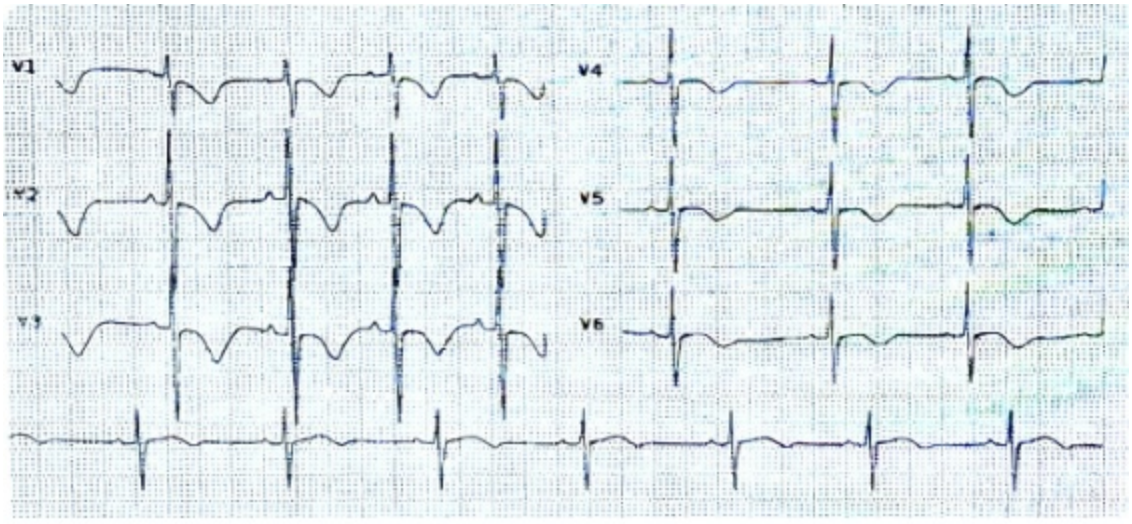


Figure 4

ST-segment depression and inverted T wave in precordial leads