

Five recurrent episodes of Takotsubo syndrome provoked by various triggers over a period of 7 years: a case report

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Background

Takotsubo syndrome (TTS), also known as stress cardiomyopathy or apical ballooning syndrome, presents as reversible regional left ventricular wall motion abnormalities in the absence of obstructive coronary artery disease. It is associated with a recurrence rate of approximately 4%. However, multiple recurrence episodes are rare in clinical settings, and the predictors of recurrence and preventive methods have yet to be fully elucidated.

Case summary

A 69-year-old woman experienced two TTS episodes before complaining of sudden-onset epigastric pain without any particular trigger. No significant coronary lesion was observed on coronary angiography, while left ventriculography showed the typical findings of apical ballooning and a hyperkinetic wall motion at the basal level of the left ventricle. The patient was again diagnosed with recurrent TTS. On Day 5 of hospitalization, follow-up echocardiography showed mural thrombus formation in the left ventricular apex. Anticoagulant therapy with oral warfarin following intravenous heparin was effective in dissolving the thrombus. She was safely discharged on Day 16 of hospitalization. However, two additional recurrent TTS episodes provoked by emotional stress occurred afterwards. Since the final hospitalization, she has been prescribed perindopril 4 mg/day and β 1-receptor-selective β -blocker bisoprolol 5 mg/day and has been able to avoid the 6th recurrence of TTS for more than 12 months at present.

Conclusion

Multiple recurrent TTS episodes are rare in the clinical setting. As such, the long-term follow-up of this case may provide clues on the pathophysiology of this disease and aid us in establishing effective preventive strategies.

Keywords

Case report • Takotsubo syndrome • Apical ballooning • Recurrence • Trigger

ESC Curriculum

2.3 Cardiac magnetic resonance • 3.1 Coronary artery disease • 3.4 Coronary angiography • 6.5 Cardiomyopathy

Learning points

- Takotsubo syndrome (TTS) is generally considered a benign disease and is associated with a favourable prognosis. However, knowledge regarding recurrent episodes is limited due to the scarcity of data.
- A variety of factors, such as negative stressors and positive emotions, can trigger TTS events.
- The predictors of recurrent TTS and its preventive methods have not yet been fully elucidated, but combination therapy (β -blocker and angiotensin-converting enzyme inhibitor/ angiotensin-II antagonist) is a promising treatment option.

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Introduction

Takotsubo syndrome (TTS), also known as stress cardiomyopathy or apical ballooning syndrome, was first described in 1990 as reversible regional left ventricular wall motion abnormalities in the absence of obstructive coronary artery disease. Its clinical presentation in the acute phase mimicks acute myocardial infarction but without the involvement of plaque rupture in the coronary artery, and the wall motion abnormalities resolve completely in most cases. Postmenopausal women are predominantly affected by this pathology that is often triggered by emotional stress or medical illness. However, the detailed mechanisms and clinical features remain controversial, including the triggers of illness and ballooning patterns. In addition, TTS is associated with a recurrence rate of approximately 4% or a rate of 0.9% patients/year.¹ However, multiple recurrence episodes are rare in clinical settings, and the predictors of recurrence and preventive methods have not yet been fully elucidated.²

Timeline

Time	Events
54 months previously	1st Takotsubo syndrome (TTS) episode after laparoscopic adrenalectomy.
8 months previously	2nd TTS episode triggered by emotional stress related to her daughter's death.
Day 1	3rd TTS onset with sudden epigastric pain, coronary angiography and left ventriculography.
Day 5	Thrombus formation in the left ventricular apex confirmed by ultrasound cardiography (UCG).
Day 14	Thrombus dissolution and improved wall motion abnormalities confirmed by UCG.
Day 16	Discharge from hospital.
4 months later	4th TTS episode triggered by emotional stress related to her daughter's death.
22 months later	5th TTS episode triggered by emotional stress related to coronavirus disease-19 pandemic

Case presentation

On the day of onset, the 69-year-old woman was eating lunch with her friends in the afternoon. However, in the evening, she complained of sudden-onset epigastric pain, and consulted our emergency room. She had two TTS previous episodes with the first episode occurring just after undergoing laparoscopic adrenalectomy for Cushing's syndrome, and the second episode being provoked by the reminiscence of her daughter's death.

Laboratory examinations revealed negative troponin T, and slightly increased brain natriuretic peptide (45.6 pg/mL; cut-off value 18.4 pg/mL). The electrocardiogram (ECG) showed sinus rhythm

with no remarkable ST-T wave changes (Figure 1A). On the other hand, the echocardiogram [ultrasound cardiography (UCG)] demonstrated an abnormal anterior-apical wall motion, but neither notable valvular dysfunction nor shunt flow was observed. Her InterTAK Diagnostic Score was calculated to be 54 points (female sex, no ST-segment depression, psychiatric disorders, and QTc prolongation).³ Following the diagnostic algorithm of TTS, we conducted left ventriculography, which showed the typical findings of apical ballooning, and hyperkinetic wall motion at the basal level of the left ventricle. The ejection fraction was 40.3% (Figure 2A and B). Coronary angiography ruled out obstructive coronary disease (Figure 2C and D). Cardiovascular magnetic resonance imaging showed the typical regional wall motion abnormality and a high-intensity signal in the short tau inversion recovery image (Figure 2E). Furthermore, there was no late gadolinium enhancement. The patient did not show any signs or symptoms that were suspicious for viral infections. The serum C-reactive protein level was within normal limits, and no pericardial effusion was detected in any imaging modality. Based on these findings, we ruled out the possibility of myocarditis and diagnosed with recurrent TTS.

On the following day, T-wave inversion in the broad range of limb and chest leads emerged on the ECG (Figure 1B). On Day 5 of hospitalization, she underwent follow-up UCG, which revealed mural thrombus formation in the left ventricular apex (Figure 3A and B). Anticoagulant therapy with oral warfarin following intravenous heparin effectively dissolved the thrombus, which was confirmed by UCG on Day 14 of hospitalization.

The blood chemical concentrations of each catecholamine were within normal limits (Figure 4A). On the other hand, ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) scintigraphy showed reduced H/M ratios of 1.59 in the early phase and 1.24 in the delayed phase, respectively. The washout rate was increased to 49.08%, suggesting decreased sympathetic function (Figure 4B).

She was haemodynamically stable, and no arrhythmic events were observed during hospitalization. She was safely discharged on Day 16 of hospitalization. However, two additional recurrent TTS episodes provoked by emotional stress occurred afterwards (Table 1). Since the final hospitalization, she has been prescribed perindopril 4 mg/day and β 1-receptor-selective β -blocker bisoprolol 5 mg/day (changed from non-selective β -blocker carvedilol after the 5th recurrent episode) and has been able to avoid the 6th recurrence of TTS for more than 12 months at present.

Discussion

The recurrence of TTS is defined as a TTS event that occurs after the complete recovery of the wall motion abnormalities related to a previous TTS event. All five TTS episodes that occurred in our case satisfied the said criteria. In the International Takotsubo Registry, recurrent TTS episodes occurred in 66 patients (4.7%) of 1402 patients at time intervals of 30 days to 9.9 years after the first episode.⁴

Considering the frequency of TTS recurrence, we have rarely encountered multiple recurrent episodes of TTS in one patient. Accordingly, there are only a few reports about cases with more than three recurrences of TTS.^{5,6} Takotsubo syndrome is usually

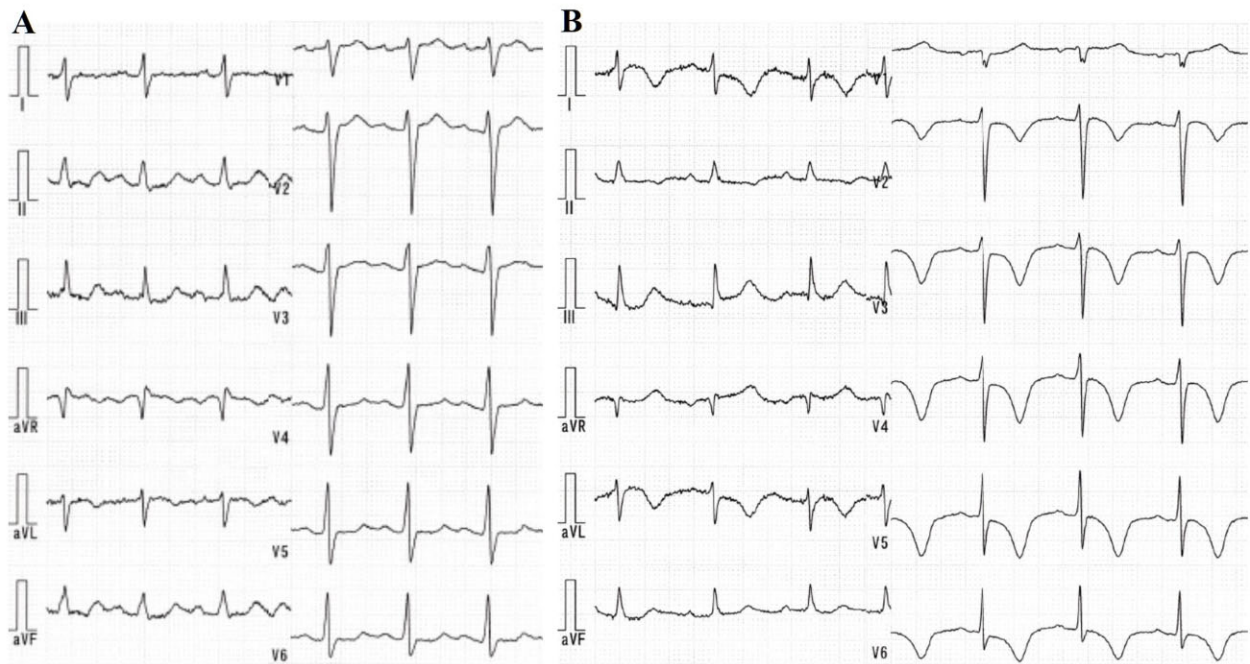


Figure 1 (A) The electrocardiogram on arrival showing a sinus rhythm and no remarkable ST-T change. (B) T-wave inversion in the broad range of the limb and chest leads on Day 2 of hospitalization.

associated with myocardial necrosis to some extent. An elevated admission troponin level is said to be a predictor of worse in-hospital outcomes. The lesser extent of cardiac damage in our case, as indicated by the negative troponin level, might have contributed to the quick recovery from TTS. In my opinion, we can make a hypothesis that these conditions might have been involved in the patient's five TTS recurrences.

During these recurrent episodes, a variety of triggering events and different patterns of ventricular involvement was reported in the same patient. A multicentre TTS registry showed that up to 20% of cases had a variable TTS pattern at recurrence.⁷ Neurogenic myocardial stunning is one of the proposed mechanisms of TTS.⁸ The myocardial uptake of ¹²³I-MIBG reflects myocardial sympathetic innervation. As such, it is reduced for months in dysfunctional segments despite the normal perfusion, consistent with regional disturbance of sympathetic neuronal activity. In our case, the affected region was always the left ventricular apex, the most typically affected region, which corresponds to the lesion with abnormal findings on ¹²³I-MIBG scintigraphy.

Regarding the triggers (physical and/or emotional) of TTS recurrence, almost half of recurrent episodes were reported to be triggered by a new stressor compared with the first TTS event. The International Takotsubo Registry showed that comorbidities such as

psychiatric and neurologic disorders were independent predictors of TTS recurrence.⁴ The triggers in each recurrent episode in our case showed varying patterns (*Table 1*). Notably, besides emotional and physical stressors, enjoyable episodes may also trigger recurrent TTS.⁹ In our case, she had a comorbidity of depression for several years, which might have affected her multiple recurrent TTS episodes.

Although patients with TTS are considered to have favourable prognoses, the recent international expert consensus document reported that the rates of serious adverse in-hospital events such as cardiogenic shock and death are comparable to acute coronary syndrome.² Common in-hospital complications include thromboembolic events, cardiogenic shock, pulmonary oedema, and arrhythmias. In our case, intraventricular thrombus formation occurred in the 3rd recurrence, which was safely resolved with anticoagulation therapy without causing any embolic events. Although serious complications caused by a single TTS episode are infrequent, repetitive TTS events will increase the risk of serious in-hospital complications. Therefore, it is important to manage these patients appropriately to avoid recurrent TTS events.

However, the prevention of TTS recurrence has not yet been established. Because TTS is associated with hyperadrenergic stimulation, patients with TTS are often prescribed β -blockers for daily use.

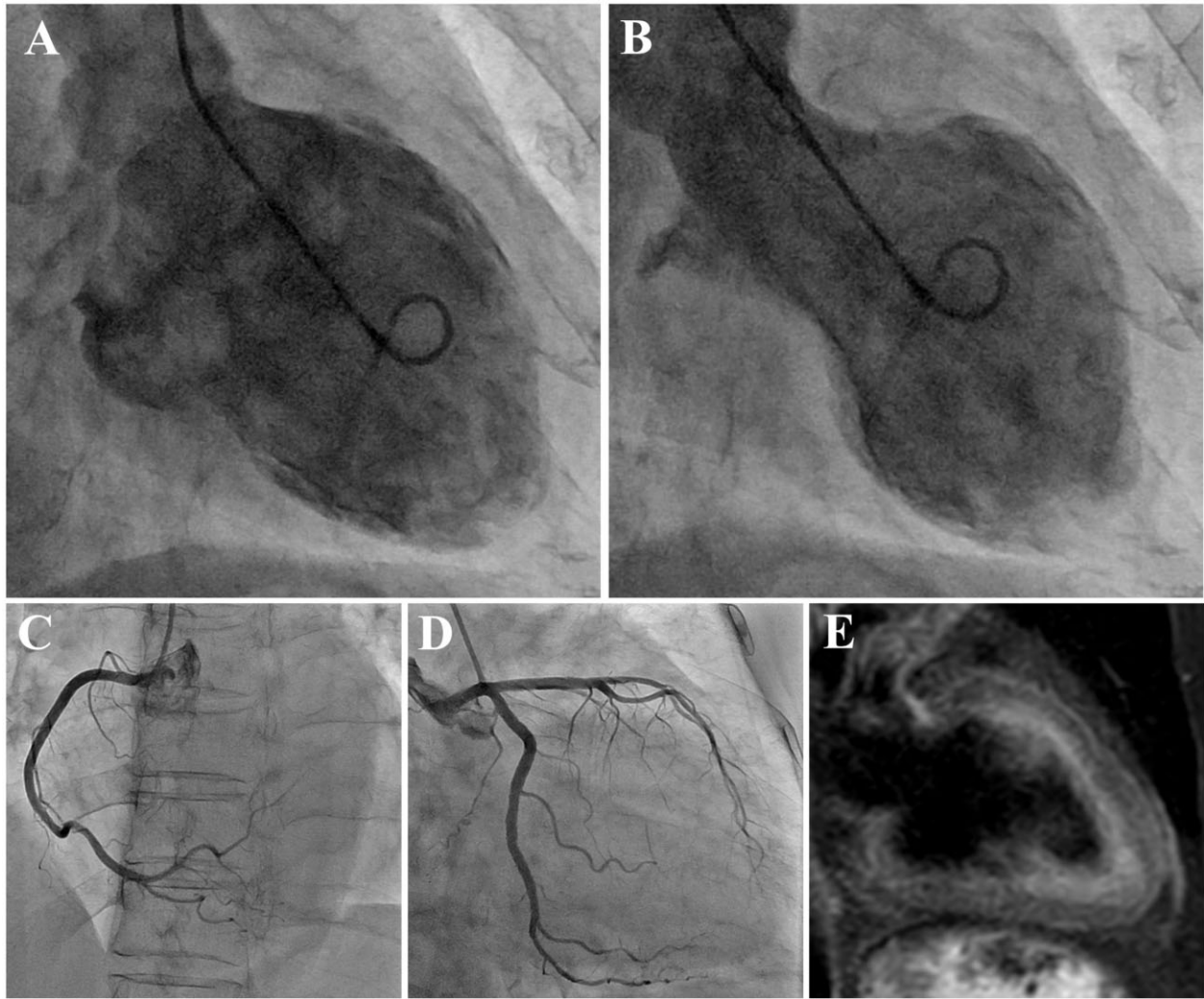


Figure 2 (A) Left ventriculography in diastolic phase. (B) Left ventriculography in systolic phase demonstrating the typical findings of apical ballooning and a hyperkinetic wall motion at the basal level of the left ventricle. The coronary angiogram showing intact coronary arteries. Right coronary artery (C). Left coronary artery from right anterior oblique caudal view (D). (E) A short tau inversion recovery image of cardiovascular magnetic resonance imaging showing high intensity at the area of regional wall motion abnormality.

On the other hand, it was reported that an angiotensin-converting enzyme inhibitor or AT-II antagonist was more effective to reduce TTS recurrence than β -blockers.¹⁰ Moreover, combination therapy might be more effective than stand-alone therapy.¹¹ Possibly, the mechanisms of effective combination therapy involve a reduction in sympathetic activity or the suppression of inflammatory reactions through interactions with the renin-angiotensin system.¹² However, a recent study demonstrated that combination therapy lacked efficacy for TTS recurrence.¹ Our case is worthwhile as the heterogeneous TTS recurrences occurred in the same individual. By continuously following up on this patient, we can compare the effect

of medicines under identical backgrounds, allowing for the identification of effective preventative strategies.

Conclusion

Over 7 years, the patient experienced five recurrent episodes of TTS that were provoked by a variety of triggers. Multiple recurrent TTS episodes are clinically rare, and the long-term follow-up of this case may provide clues on the pathophysiology of this disease and aid us in establishing effective preventive strategies.

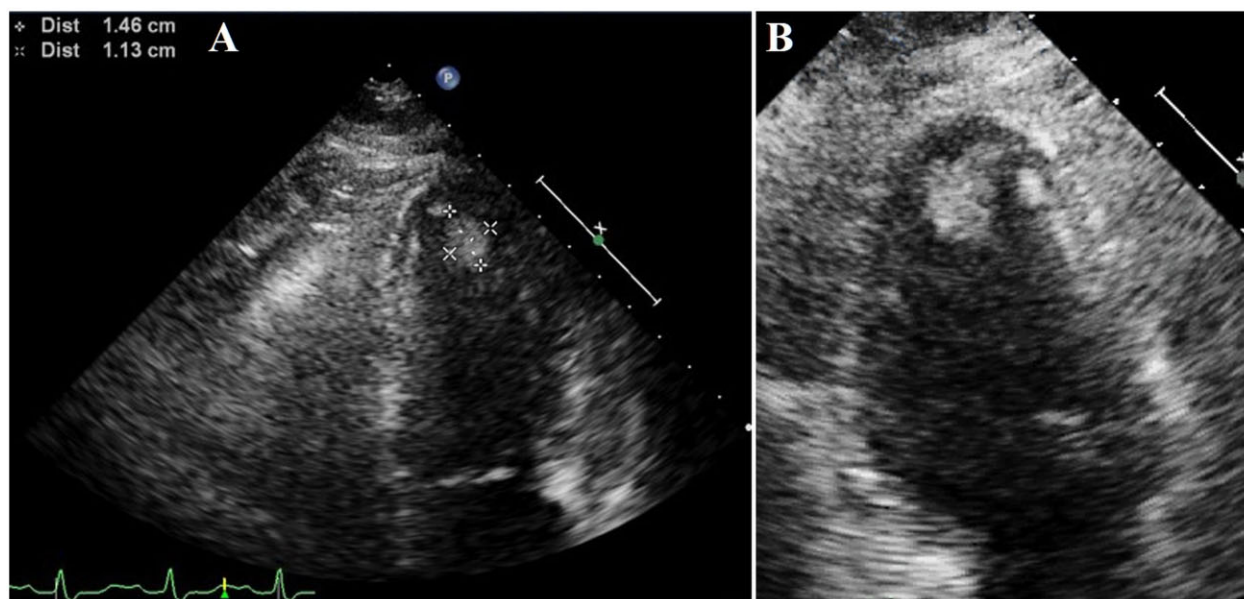


Figure 3 (A) Ultrasound cardiography showing mural thrombus formation (1.46 × 1.13 cm) in the left ventricular apex on Day 5 of hospitalization. (B) Magnified image of the apex.

A		Reference	Measured value
Adrenaline	(pg/mL)	0-100	<5
Noradrenaline	(pg/mL)	100-450	157
Dopamine	(pg/mL)	0-20	<5
5-HIAA	(ng/mL)	1.8-6.1	5.6
VMA	(ng/mL)	3.3-8.6	7.2
HVA	(ng/mL)	4.4-15.1	8.3

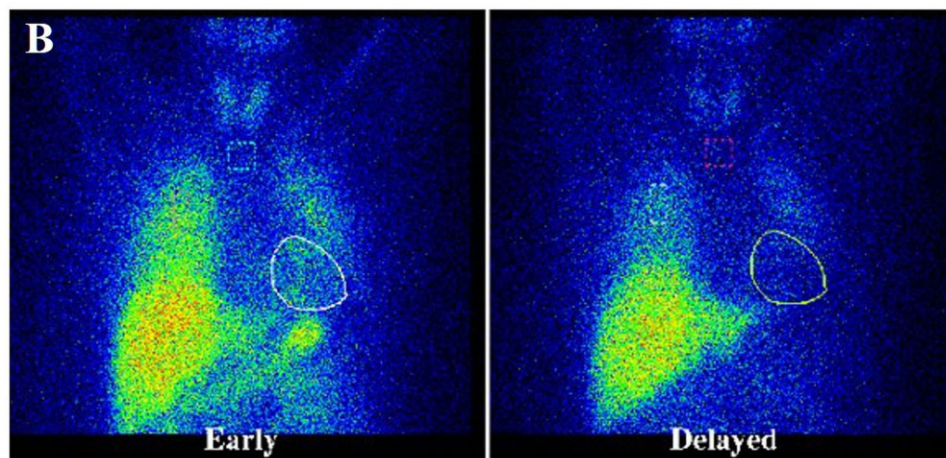


Figure 4 (A) Blood chemical concentrations of each kind of catecholamine, all within normal limits. (B) ^{123}I -metaiodobenzylguanidine scintigraphy suggesting a decreased sympathetic function.

Table 1 Clinical presentation of a 69-year-old female with five recurrent episodes of TTS

Event of hospitalization	1st	2nd	3rd	4th	5th
Duration from initial episode (months)		46	54	58	76
Symptoms	Dyspnoea	Chest squeezing	Epigastric pain	Anterior chest pain	Chest squeezing
Trigger	Laparoscopic adrenalectomy	Emotional stress related to family death	No trigger	Emotional stress related to family death	Emotional stress related to COVID-19 pandemic
ACE-I/ARB/ β -blocker at onset	Candesartan 8 mg	Perindopril 4 mg	Perindopril 4 mg	Perindopril 4 mg	Perindopril 4 mg + Carvedilol 20 mg
ECG on admission	T-wave inversion ST-segment depression QTc prolongation	QTc prolongation	QTc prolongation	QTc prolongation	T-wave inversion ST-segment depression
InterTAK diagnostic score (points)	55	78	54	78	60
Qualitative troponin T	Negative	Negative	Negative	Negative	Negative
BNP (pg/mL)	118.8	78.2	45.6	41.4	58.6
Wall motion abnormality	Hypokinesia at the apex	Apical ballooning	Apical ballooning	Apical ballooning	Hypokinesia at the apex
EF (%)	52.4	40.9	40.3	39.9	50.0
Timing of confirmed wall motion recovery (days)	6	6	14	14	4
Hospitalization (days)	16	7	16	23	5
Complication	None	None	Ventricular thrombus	None	None

Lead author biography



Tetsuya Nomura graduated from Kyoto Prefectural University of Medicine in 1999 and completed doctoral course in medicine in 2007. Currently, he is a director in the Department of Cardiovascular Medicine in Kyoto Chubu Medical Center. He specializes in interventional cardiology and endovascular treatment.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report, including the images and associated text, has been obtained from the patient in line with COPE guidance.

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