

CASE REPORT

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A case report of psychiatric symptoms following direct-acting antiviral and ribavirin combination therapy for chronic hepatitis C in a patient with innate anxiety

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Abstract

Background: Direct-acting antivirals (DAAs) result in a highly sustained virological response rate and better patient tolerance. However, this therapeutic approach may, on rare occasions, give rise to psychiatric symptoms. We describe a case requiring discontinuation of DAA and ribavirin combination therapy due to psychiatric symptoms in a patient with congenital anxious personality traits. The information summarized here will be helpful to physicians treating chronic hepatitis C virus (HCV) infection in patients with underlying psychiatric problems.

Case presentation: A 57-year-old Japanese woman diagnosed with chronic HCV infection was prescribed DAA and ribavirin combination therapy. She had a history of mild innate anxiety and development of psychiatric symptoms due to interferon (IFN) therapy 8 years prior, which subsided with discontinuation of the therapy. Similar psychiatric symptoms such as enervation, palpitations, an episode of hyperventilation, and consciousness disturbances with myotonia were observed after the administration of the antiviral agents. No abnormal findings related to her symptoms were observed on laboratory or imaging results. Psychiatrists diagnosed the patient as having a somatization disorder induced by the antiviral agents on the basis of innate anxiety. After the discontinuation of therapy, her symptoms gradually improved.

Conclusions: Although DAAs were not causative factors for psychiatric symptoms in phase 3 studies, a post-marketing study reported psychiatric symptoms such as depression in patients with underlying psychiatric problems. Our case suggests psychiatric symptoms might worsen after DAA and ribavirin administration in patients with underlying psychiatric disorders, and therefore, close monitoring is necessary for these patients, especially if they have a history of psychiatric symptoms after IFN.

Keywords: Interferon, Direct-acting antiviral, Psychiatric symptom, Case report

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Background

Chronic hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease, and approximately 2.2% of adults worldwide are infected [1]. In addition, 10–15% of these cases progress to liver cirrhosis and hepatocellular carcinoma, leading to a fatal outcome [2–4]. The first established therapy for hepatitis C was interferon (IFN) reported by Hoofnagle et al. in 1986, wherein administration of human recombinant IFN- α resulted in normalization of transaminases in patients with non-A, non-B hepatitis [5]. IFN- α monotherapy (thrice weekly, 6 million international units per day) resulted in sustained virological response (SVR) of only 5% in resistant cases such as genotype 1 with high viral ribonucleic acid levels; therefore, the development of PEGylated IFN (PEG-IFN) and ribavirin combination therapy contributed to the increase in SVR rates (approximately 42–56%) [6, 7]. Thus, IFN and its combination therapies significantly decreased the occurrence of hepatocellular carcinoma and improved prognoses [8]. Conversely, in some cases, PEG-IFN and ribavirin combination therapy induces various adverse events including cytopenia, influenza-like, gastrointestinal, and psychiatric symptoms that may require discontinuation of the therapy [6, 7].

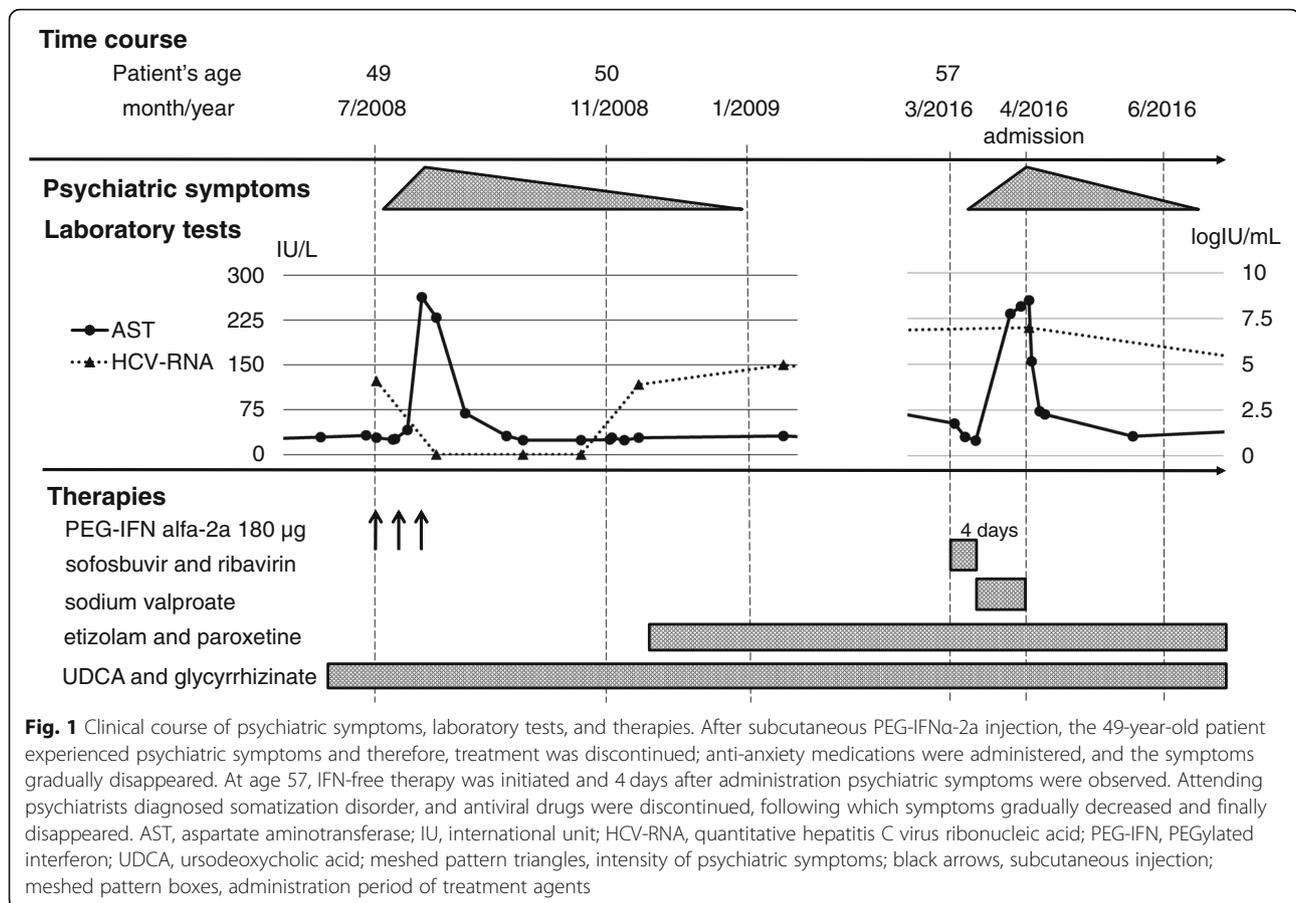
HCV treatment paradigms have dramatically shifted with the development of direct-acting antivirals (DAAs) that provide SVR rates as high as 80–100% and with better patient tolerance [9]. However for a portion of IFN-intolerant patients, psychiatric adverse effects have thwarted efforts using DAA therapy. In this report, we present the case of an innate anxiety patient with a history of IFN discontinuation due to psychiatric symptoms and who developed similar symptoms using DAA and ribavirin to treat her HCV hepatitis. The information summarized is intended for physician awareness of possible drawbacks of IFN-free treatment for HCV infection in patients with underlying psychiatric issues.

Case presentation

A 49-year-old Japanese woman was presented with chronic hepatitis due to HCV genotype 2 infection. She had a psychiatric history of mild innate anxiety but was not medicated. She was prescribed subcutaneous injection of PEG-IFN α -2a at a dose of 180 μ g per week to treat chronic hepatitis. After initiation of therapy, a low-grade fever and mild general fatigue were observed. Psychiatric symptoms such as enervation, palpitations, an episode of hyperventilation, and consciousness disturbances with myotonia appeared after the third injection of PEG-IFN α -2a. It was impossible to decide if the symptoms were IFN-related or due to a somatization disorder elicited by anxiety, but the IFN therapy was discontinued and followed by administration of etizolam

and paroxetine hydrochloride hydrate treatment by psychiatrists. Although the symptoms gradually improved, it took 3 months for the patient to completely recover (Fig. 1); the anti-anxiety medications were continued for a prolonged period. While waiting for approval of DAA therapy, the patient was administered liver supporting therapies: oral ursodeoxycholic acid and glycyrrhizinate. Upon approval, the patient was administered with IFN-free sofosbuvir and ribavirin combination therapy. She was 57 years at this time point and 8 years had elapsed since the PEG-IFN therapy. The patient remained diagnosed with chronic hepatitis, as she showed a low score of 2.50 in the fibrosis-4 index [10] and aspartate aminotransferase-to-platelet ratio index [11] was 0.731. Unexpectedly, psychiatric symptoms similar to those observed with IFN and consciousness disturbance attacks appeared 4 days after treatment initiation. Initially, psychiatrists attributed the symptoms to epileptic seizures, and sodium valproate was administered. However, her symptoms did not improve, and the patient was admitted for further observation and treatment.

Physical examination was unremarkable. The liver and spleen were not palpable, and her bowel sounds were normal. Anemia and jaundice were not seen in palpebral conjunctiva or bulbar conjunctiva. Flapping tremor and leg edema were absent. Abnormal neurological findings were not detected. The patient denied alcohol and/or drug abuse. Upon admission, the patient was administered etizolam and paroxetine for anxiety disorder, ursodeoxycholic acid and glycyrrhizinate for chronic hepatitis, and metoprolol and enalapril for chronic heart failure after a surgical operation for endocardial cushion defect. Other than a mild increase in serum aspartate and alanine aminotransferase levels due to sodium valproate administration, no abnormal laboratory findings, including ammonium or glycemic levels that might induce consciousness disturbances, were found (Table 1). There was no evidence for HBV and HIV co-infection. Furthermore, the patient's electroencephalogram and brain magnetic resonance imaging findings were normal (Fig. 2a-c). These results indicated no evidence of infection or hepatic or drug-induced encephalopathy. In addition, the patient had stable vital signs and communicated well even during the psychiatric attacks unless prompted about hepatitis related topics (which would not have been the case if she was suffering from epileptic seizures). Based on the clinical picture, psychiatrists confirmed a diagnosis of somatization disorder induced by anxiety from antiviral therapy. Sodium valproate, sofosbuvir, and ribavirin were discontinued, and her symptoms gradually disappeared after 3 months. Anti-anxiety medication was continued for treatment of the somatization disorder; the patient continued to receive liver supporting therapies because of a mild increase in



serum aspartate and alanine aminotransferase levels; interruption of antiviral therapy showed no clearance of HCV. With the combination of mental health support from psychiatrists, we are planning to retry an alternate DAA regimen without ribavirin.

Discussion and conclusions

A meta-analysis of HCV patients demonstrated evidence for high incidence rates of depression and/or anxiety even in untreated patients [12]. It is well known that IFN therapy precipitates psychiatric symptoms such as depression, irritability, anxiety, agitation, loss of appetite, fatigue, sleep disturbance, and impaired cognition; it is difficult to distinguish underlying symptoms from IFN-related ones [13]. Risk factors for IFN-related psychiatric symptoms include the following: high dose of IFN, older age, history of organic brain syndrome, current psychiatric diseases, or depression or insomnia, drug abuse, and disease or therapy anxiety [14]. IFN-related psychiatric adverse events lead to discontinuation of therapy or hospital admission in 10% of cases, whereas 30% of cases continue IFN therapy with supportive therapy such as anti-depressant or anti-anxiety medication [15, 16]. In

several patients with psychiatric symptoms, intolerance to IFN resulted in the future of HCV elimination.

DAA therapy, on the other hand, is associated with high SVR rates and better patient tolerance, especially for psychiatric symptoms, as reported in a phase 3 study that excluded patients with underlying psychiatric disorders [9]. Ledipasvir and sofosbuvir combination therapy showed SVR rates of 99%, with no discontinuation owing to adverse events and no treatment-related depression [17]. Similarly, high SVR rate and fewer adverse events were reported with DAA combination therapy with ribavirin for HCV genotype 2 patients [18]. However, in a phase 4, open-label study, 6.1% of patients with liver cirrhosis, reported depression and an equal rate of insomnia in a patient population where 35% suffered from underlying depression, 30% from underlying anxiety or anxiety disorder, and 10% from alcohol abuse [19]. Takeda et al. reported a mild increase in depression in the first 4 weeks after administration of DAAs, which recovered within 12 weeks [20], as revealed by the Beck Depression Inventory scores, which are calculated by a 21-question multiple-choice self-application instrument to assess the severity of depression [21]. The authors suggested that anxiety associated with antiviral treatment

Table 1 Laboratory data on admission with psychiatric symptoms after sofosbuvir and ribavirin combination IFN-free therapy

Hematology		Normal Value	Biochemistry		Normal Value
Leukocyte count (/mm ³)	3370	3300–8600	Total Protein (g/dl)	7.2	6.6–8.1
Erythrocyte count (× 10 ⁴ /mm ³)	450	386–492	Albumin (g/dl)	3.8	4.1–5.1
Hemoglobin (g/dl)	13.7	11.6–14.8	Serum sodium (mEq/l)	140	138–145
Hematocrit (%)	42.3	35.1–44.4	Serum potassium(mEq/l)	3.8	3.6–4.8
Platelet count (× 10 ⁴ /mm ³)	10.2	15.8–34.8	Serum chloride(mEq/l)	104	101–108
Coagulation test			Serum IP (mg/dl)	3.1	2.5–4.5
Prothrombin time (%)	93	70–130	Serum calcium (mg/dl)	9.5	8.8–10.1
PT-INR	1.04	1.0	Total bilirubin (mg/dl)	0.6	0.4–1.5
Tumor marker			Direct bilirubin (mg/dl)	0.1	< 0.3
			AST(IU/l)	255	13–30
			ALT(IU/l)	434	7–23
α-fetoprotein (ng/ml)	3	< 9.5	LDH (IU/l)	252	124–222
AFP-L3(%)	< 0.5	< 10.0	ALP(IU/l)	376	106–322
Viral marker			GGT(IU/l)	81	9–32
HCV-Ab	positive	negative	Blood urea nitrogen(mg/dl)	12	8–20
HCV serotype	2		Creatinine (mg/dl)	0.60	0.46–0.79
HCV-RNA (logIU/ml)	7.0	negative	Fasting blood sugar (mg/dl)	132	
HBsAg	negative	negative	Serum ammonia (μl/dl)	47	12–66
HIV-Ab	negative	negative	C-reactive protein (mg/dl)	0.01	< 0.15
			Thyroid hormone		
			Free triiodothyronine (pg/ml)	3.5	2.3–4.0
			Free thyroxine (ng/dl)	1.3	0.9–1.7

Abnormal values are given in bold type

PT-INR, international normalized ratio of prothrombin time; AFP-L3, *Leus culinaris* agglutinin a-reactive α-fetoprotein; HCV-Ab, hepatitis C virus-antibody; HCV-RNA, quantitative hepatitis C virus-ribonucleic acid; HBsAg, hepatitis B surface antigen; HIV-Ab, human immunodeficiency virus-antibody; IP, inorganic phosphorus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase

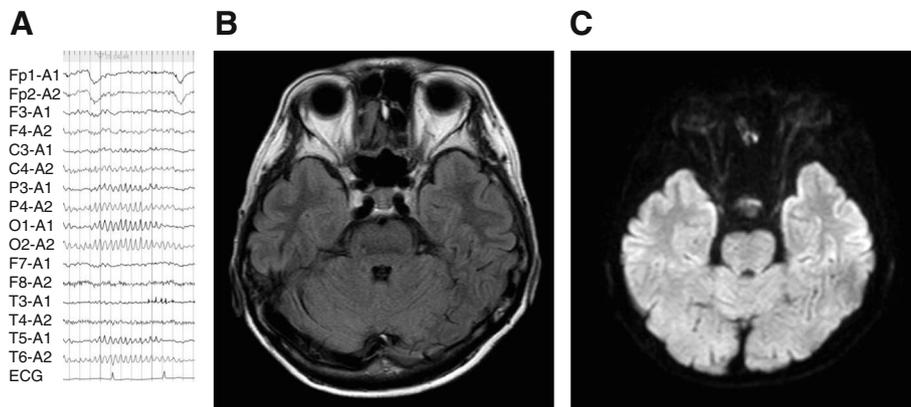


Fig. 2 Imaging findings on admission with psychiatric symptoms after interferon-free therapy. Electroencephalogram showed 10–11 Hz with an irregular unsteady α wave dominant in the occipital lobe and without paroxysmal abnormality (a). Brain magnetic resonance imaging in fluid-attenuated inversion recovery (b) and diffusion-weighted imaging (c) revealed normal findings, and drug-induced encephalopathy was not developed

might worsen depression scores, regardless of the regimen, which is consistent with the clinical course observed in our case. Although, to our knowledge, DAAs do not directly affect the central nervous system, Volpato et al. reported DAAs may have mild neurotoxicity in patients with LC, because of increased relative delta power in the electroencephalogram at the end of treatment with DAAs [22]. Conversely, Sundberg et al. reported no increase in depression scores on other self-rating scales after DAA therapy [23]. Further studies are required to determine whether DAAs affect the central nervous system and manifest psychiatric symptoms, since patients with underlying psychiatric disorders are sensitive to psychiatric adverse events associated with DAA therapy.

Furthermore, ribavirin may worsen the psychiatric symptoms. Ribavirin combination therapy with both PEG-IFN [6] and DAA [24] significantly increased not only anemia, but also psychiatric symptoms such as fatigue and insomnia compared with PEG-IFN or DAA monotherapy.

In conclusion, psychiatric disease is common among patients with chronic HCV infection, and those undergoing IFN-based treatment, but our case signals the possibility of psychiatric effects with oral DAA regimens as well. Therefore, close monitoring is necessary for patients who have psychiatric risk factors similar to IFN-related psychiatric symptoms, such as history of depression, insomnia, or anxiety to disease or medication, and who are undergoing IFN-free therapy, especially ribavirin combination regimens.

Abbreviations

DAA: Direct-acting antiviral; HCV: Hepatitis C virus; IFN: Interferon; PEG-IFN: PEGylated interferon; SVR: Sustained virological response

Acknowledgements

Not applicable.

Authors' contributions

AS, KK, NS, KT, and KM contributed to treatment for hepatitis. NF, HW, TSu, and TSo contributed to diagnosis and treatment for psychiatric symptoms. AS wrote the manuscript. MT, HK, SY, and ST critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Authors' information

Not applicable.

Funding

The authors have no funding to report.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

This case report did not require the review by the Institutional Review Board of Graduate School of Medical and Dental Sciences, Niigata University.

Consent for publication

A written informed consent was obtained for publication from the patient.

Competing interests

The authors declare that they have no competing interests.

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Received: 29 November 2017 Accepted: 6 June 2019

Published online: 13 June 2019

References

- Global Burden Of Hepatitis C Working Group. Global burden of disease (GBD) for hepatitis C. *J Clin Pharmacol.* 2004;44:20–9.
- Seeff LB, Hoofnagle JH. Appendix: the National Institutes of Health consensus development conference Management of Hepatitis C 2002. *Clin Liver Dis.* 2003;7:261–87.
- Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT study group. Inhibition of Hepatocarcinogenesis by interferon therapy. *Ann Intern Med.* 1999;131:174–81.
- Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol.* 2010;52:652–7.
- Hoofnagle JH, Mullen KD, Jones DB, et al. Treatment of chronic non-a, non-B hepatitis with recombinant human alpha interferon. A preliminary report. *N Engl J Med.* 1986;315:1575–8.
- Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med.* 2002;347:975–82.
- Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet.* 2001;358:958–65.
- Ikeda K, Saitoh S, Arase Y, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology.* 1999;29:1124–30.
- Maan R, van Tilborg M, Deterding K, et al. Safety and effectiveness of direct-acting antiviral agents for treatment of patients with chronic hepatitis C virus infection and cirrhosis. *Clin Gastroenterol Hepatol.* 2016;14:1821–30.
- Vallet-Pichard A, Mallet V, Verkarre V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology.* 2007;46:32–6.
- Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology.* 2003;38:518–26.
- Schaefer M, Capuron L, Friebe A, et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. *J Hepatol.* 2012;57:1379–90.
- Pinto EF, Andrade C. Interferon-related depression: a primer on mechanisms, treatment, and prevention of a common clinical problem. *Curr Neuropharmacol.* 2016;14:743–8.
- Okanoue T, Sakamoto S, Itoh Y, et al. Side effect of high-dose interferon therapy for chronic hepatitis C. *J Hepatol.* 1996;25:283–91.
- Hosoda S, Takimura H, Shibayama M, Kanamura H, Ikeda K, Kumada H. Psychiatric symptoms related to interferon therapy for chronic hepatitis C: clinical features and prognosis. *Psychiatry Clin Neurosci.* 2000;54:565–72.
- McNutt MD, Liu S, Manatunga A, et al. Neurobehavioral effects of interferon- α in patients with hepatitis-C: symptom dimensions and responsiveness to paroxetine. *Neuropsychopharmacology.* 2012;37:1444–54.
- Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med.* 2014;370:1889–98.
- Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med.* 2014;370:1993–2001.
- Ho SB, Monto A, Peyton A, et al. Efficacy of Sofosbuvir plus ribavirin in veterans with hepatitis C virus genotype 2 infection, compensated cirrhosis, and multiple comorbidities. *Clin Gastroenterol Hepatol.* 2017;15:282–8.
- Takeda K, Noguchi R, Namisaki T, et al. Therapeutic effect of dual oral therapy with daclatasvir and asunaprevir for chronic HCV patient with depression. *Kanzo (Journal of the Japan Society of Hepatology).* 2016;57:496–8 in Japanese.

21. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561–71.
22. Volpato S, Montagnese S, Zanetto A, et al. Neuropsychiatric performance and treatment of hepatitis C with direct-acting antivirals: a prospective study. *BMJ Open Gastroenterol*. 2017;4(1):e000183.
23. Sundberg I, Lannergård A, Ramklint M, et al. Direct-acting antiviral treatment in real world patients with hepatitis C not associated with psychiatric side effects: a prospective observational study. *BMC Psychiatry*. 2018;18:157.
24. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med*. 2015;373:2608–17.

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