J Forensic Sci, Nov. 2002, Vol. 47, No. 6
Paper ID JFS2002102_476
Available online at: www.astm.org

CASE REPORT

S. Sannohe,[1] *M.D.; Y. Makino,*[1] *M.D.; T. Kita,*[1] *Ph.D.; N. Kuroda,*[1] *M.D.; and T. Shinozuka,*[2] *Ph.D.*

Colchicine Poisoning Resulting from Accidental Ingestion of Meadow Saffron (*Colchicum Autumnale*)

ABSTRACT: A rare case of colchicine poisoning resulting from accidental ingestion of meadow saffron (*Colchicum Autumnale*) is reported. The plant can frequently be found in the woods of the Northern Hemisphere (1), also in Japan. A 48-year-old male was admitted to hospital complaining of vomiting, nausea and diarrhea following ingestion of the plant and died in four days. The most striking histological findings were metaphasic mitotic figures in the mucosa of the large intestine and the liver. Colchicine was detected in the bile with high-performance liquid chromatography/sonicspray ionization mass spectrometry (HPLC/SSI-MS).

KEYWORDS: forensic science, colchicine poisoning, *colchicum autumnale,* accidental ingestion, pathology, toxicology

We present here a rare case of colchicine poisoning resulting from accidental ingestion of meadow saffron (*Colchicum Autumnale*). Colchicine is a lipid-soluble alkaloid obtained from the meadow saffron (2–7) or "autumn crocus" and has been the medicine of choice as a prophylactic agent against acute gouty arthritis (8–10). This plant can frequently be found in fields early in the spring and can be easily confused with edible plants such as leek or wild garlic. This plant is an uncommon but potentially serious source of acute intoxication (11). Fatal cases resulting from accidental ingestion of this plant are rare (4), while intoxications with colchicine are a well-known and frequently lethal complication of the therapy with this medicine.

Case Report

A 48-year-old man who had no access to medical colchicine preparations, and no complaint of subjective symptoms of heart disease, collected a plant that he regarded to be *Allium victorialis platyphyllum,* which grows in the northeast area of Japan in spring. However, the plant he collected was meadow saffron (Fig. 1), which was growing in the neighborhood of his house and which very much resembles *Allium victorialis platyphyllum.* He brought the plant home and at night ate some of it with Chinese noodles (the leftover of the plant was identified as meadow saffron by the police). Approximately 3 h after the ingestion, he started complaining about nausea and repeated vomiting and diarrhea. He received medical treatment at a nearby hospital on the first and the second day based on a diagnosis of acute hepatitis or food poisoning, but the symptoms did not improve. He was admitted to hospital on the third day and was found to be dehydrated and had abdominal tenderness on examination. Infusion therapy was started from this day. The results of laboratory examination at the time of the hospitalization were as follows (in SI units): white blood count 2.2×10^9/L, red blood count 5.23×10^{12}/L hemoglobin 173 g/L, hematocrit 0.477L, platelet count 60×10^9/L, AST 281 U/L, ALT 84 U/L, PT 11.1 sec, APTT 37.5 sec, ALP 396 U/L, LDH 3753 U/L, gamma-GTP 52 U/L, T-Ch 8.66 mmol/L, TG 180.9 mmol/L, BUN 22.5 mmol/L, Cre 79.6 mol/L, UA 701.9 mol/L, Na^+ 129 mmol/L, K^+ 3.0 mmol/L, Cl^- 96 mmol/L. Even after hospitalization he continuously complained of nausea and midepigastric pain, but physical examination was unremarkable. The blood glucose level rose to 280 mg/dL on the day following admission. During the night of the second day after admission, a nurse found him collapsed and unresponsive in the hospital rest room. He expired despite 50 min of resuscitation effort. Death occurred about four days after the accidental ingestion of meadow saffron. He had not had any oral intake since the onset of symptoms.

Autopsy Findings

Postmortem examination was performed about 17 h after death; the body weight was 66 kg and height was 166 cm. Obvious rigor mortis was observed in all the joints. Postmortem hypostasis was moderately developed.

The heart, weighing 530 g with moderate hypertrophy of the left myocardium, showed multiple petechiae at the epicardium. The liver was yellowish, congested and weighed 2440 g. The intestinal tract was markedly distended with gas and fluid. The small intestine contained about 680 mL of yellow-brown turbid fluid, and the large intestine contained about 650 mL of fluid. There was no mechanical obstruction in the intestine. The brain, weighing 1650 g,

[1] Department of Forensic Medicine, Hirosaki University School of Medicine, Zaifu-cho 5, Hirosaki, Aomori 036-8562, Japan.
[2] Department of Legal Medicine, School of Medicine, Keio University, Shinanomachi 35, shinjuku-ku, Tokyo 160-8582, Japan.

Received 15 March 2002; and in revised form 22 May 2002; accepted 31 May 2002; published 18 Sept. 2002.

and each kidney, weighing 200 g, were moderately congested. Autopsy revealed massive edema and moderate congestion of the lungs. All tissues were fixed in 10% formalin, paraffin-embedded, sectioned, and stained with hematoxylin-eosin using a standard technique. The bile was sent to the Department of Legal Medicine, School of Medicine, Keio University in Tokyo for toxicological examination using HPLC/SSI-MS.

FIG. 1—*Leftover of the collected plant. Leaves and cormes of meadow saffron (colchicum autumnale).*

Analytical Details

Chromatographic System

HPLC/SSI-MS was performed on a HITACHI M-8000 LC/3DQ/MS system (Hitachi, Japan). The SSI operating parameters were: plate temperature, 230°C; aperture temperature one, 150°C; aperture temperature two, 120°C; drift voltage, 80 V; positive mode. The column used for LC/MS was Mightysil RP-18 (150 mm, 2.0 mm inside diameter, 5 m). The mobile phase was 10 mM ammonium acetate (pH 5.0)—methanol—acetonitrile (63:5:32, v/v/v), and the flow rate of the mobile phase was 0.2 mL/min. The separation was carried out at 35°C.

Extraction Method for HPLC/SSI-MS

Aliquots of 1 mL bile were mixed with 1 mL of saline and 0.4 mL of 1 M phosphate buffer (pH 7.5). The extraction was performed twice with 5 mL of chloroform and the mixture was centrifuged at 1500 rpm for 10 min. The chloroform extracts were combined and then dehydrated, and concentrated. The residue was dissolved in 500 μL of methanol and 5.0 μL was injected into the HPLC/SSI-MS.

Results

Confirmation of colchicine overdose was obtained by pathology at the microscopic level by the detection of numerous mitotic figures and chromatin bodies within organs with rapid rates of cell proliferation, such as the gastrointestinal tract and the liver.

The most conspicuous histological changes were found in the colon and the liver which are the organs with a rapid cellular turnover. In the colon, epithelial cells within the crypts of Lieberkuhn were remarkable for their detachment and loss of polarity. The nuclei of these cells appeared enlarged and hyperchromatic. Frequent mitosis and the "colchicine-figures or -bodies" (4,8) which are cells with chaotic dispersion of chromosomes within the cytoplasm were noted (Fig. 2). Examination of the

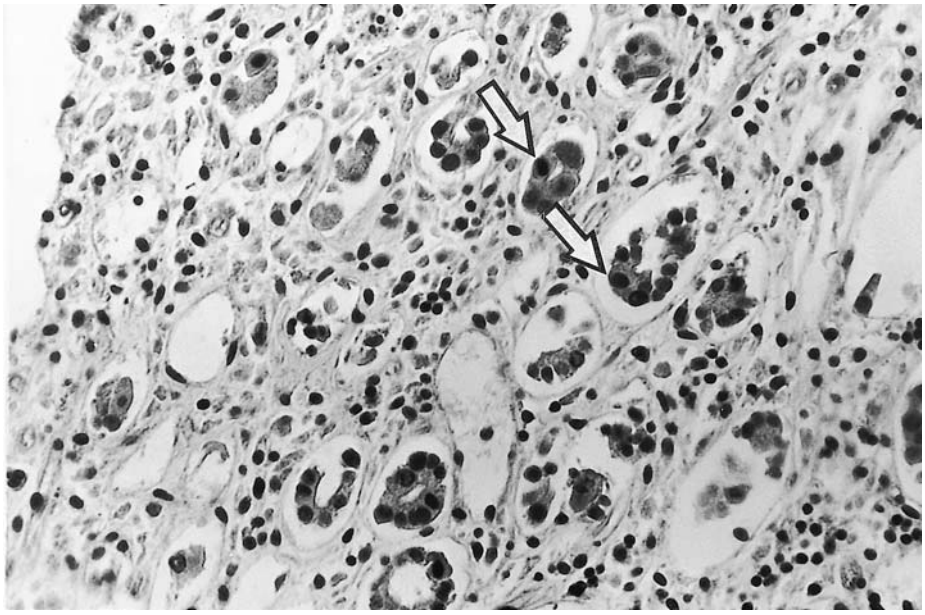

FIG. 2—*Colon: Sloughing of the surface epithelium with collapse of the crypts of Lieberkuhn is noted. Some nuclei appear hyperchromatic. Chromatin figures are indicated by the arrows (×100).*

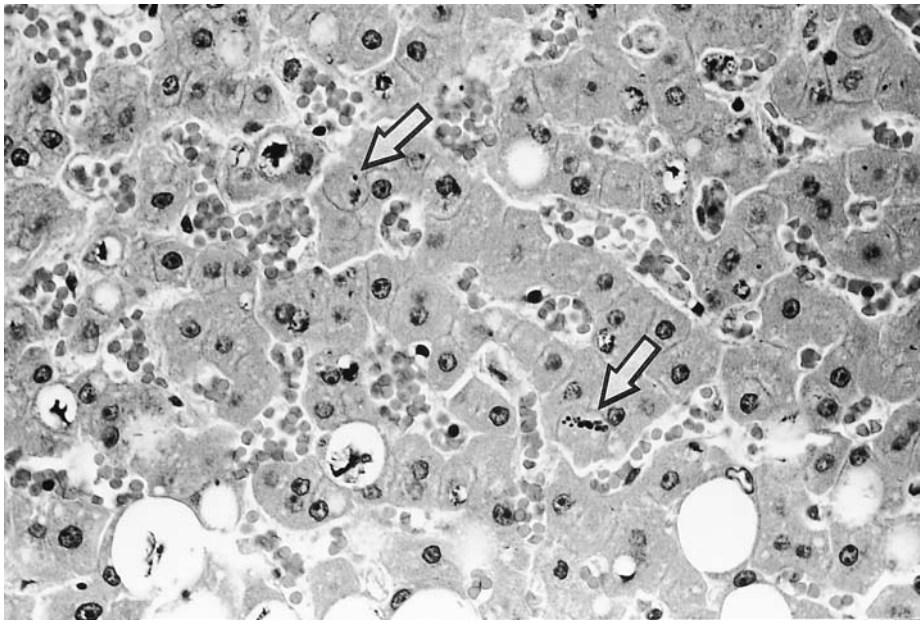

FIG. 3—*Liver: Fatty changes and mitosis figures (arrows) are observed in the liver (×50).*

liver also revealed some cells with arrested mitosis and fatty changes (Fig. 3). The spleen showed disruption of the white pulp and congestion of the red pulp. Histological evaluation of the mucosa of the stomach and the small intestine was difficult because extensive autolysis had already occurred. A total ion chromatogram (TIC) and HPLC-mass chromatogram (m/z 400) of the extract from the bile are shown in Figs. 4*a* and 4*b*. Peak 1 in the mass chromatogram gave a molecular ion peak at m/z 400 (Fig. 4*c*), which was the same molecular ion peak as the colchicine standard (Figs. 4*d* and 4*f*).

Discussion

There are a few case reports of poisoning in which leaves and stems of the plant were mixed in salad or used as a spice by mistake (4). Some clinical symptoms provide clues for making a clinical diagnosis in a case where a person possesses colchicine tablets for medical treatment. But if meadow saffron is accidentally and unknowingly ingested, it might be difficult to diagnose colchicine poisoning because the symptoms are liable to be misdiagnosed as food poisoning or other acute gastrointestinal diseases (6). Thus, serious problems can be missed or ignored completely unless the physician is aware of the potential for toxicity. The signs and symptoms of colchicine intoxication have recently been reviewed by some clinical groups (3,6,12,13) and can be characterized as having three phases as shown in Table 1.

Administration of an overdose of colchicine is accompanied by side effects, the most common being abdominal pain, nausea, vomiting and diarrhea with a massive loss of fluid and electrolytes.

The clinical course described in our case, who survived the first two stages, is consistent with that reported in the literature describing colchicine poisoning. The laboratory examinations demonstrated hypovolema, electrolyte balance disorders and disturbance of liver function. Depression of the bone marrow, which is also a known toxic effect of colchicine, was demonstrated clinically in our case by the presence of mild thrombocytopenia and leukopenia in the peripheral blood.

Tissues with a high rate of cell division, such as the bone marrow and gastrointestinal epithelium, are severely affected (4,5,8,9) because colchicine destroys the microtubules that make up the spindle apparatus (3–9). It is well recognized that colchicine exerts a toxic effect on living cells which results in the arrest of mitosis at an early stage, usually in the metaphase with production of bizarre and abnormal nuclear configurations (7), which often lead to cell death. Disturbance of water and electrolyte balance due to damage to the mucosa of the gastrointestinal tract was considered the cause of the diarrhea followed by dehydration and hypovolema. Abnormalities in the release of several neurotransmitters from the bowel wall (7) can be associated with diarrhea and ileus, and stimulation of the parasympathetic nervous system and enteric nervous system (7) also can be associated with diarrhea and ileus. The proximate cause of death in this case was considered to be dehydration and disturbed electrolyte balance caused by acute diarrhea and ileus, with aggravation of heart function. A significant route of excretion of colchicine and its metabolites are via the bile fluid (14). Consequently, the mucosal cells may be exposed to the highest and/or prolonged levels of colchicine (9) because of its enterohepatic circulation (2,14) and its secretion by the intestinal cells.

The accurate quantity of ingested meadow saffron was uncertain in this case. But the clinical symptoms, the autopsy findings, and the results of the analysis led us to conclude that the colchicine was the agent responsible for the death of the patient. This case illustrates an uncommon but potentially severe colchicine poisoning resulting from accidental ingestion of meadow saffron.

Acknowledgments

The authors extend their utmost thanks to Dr. Yutaka Tsutsumi for his helpful advice on pathology findings in this case.

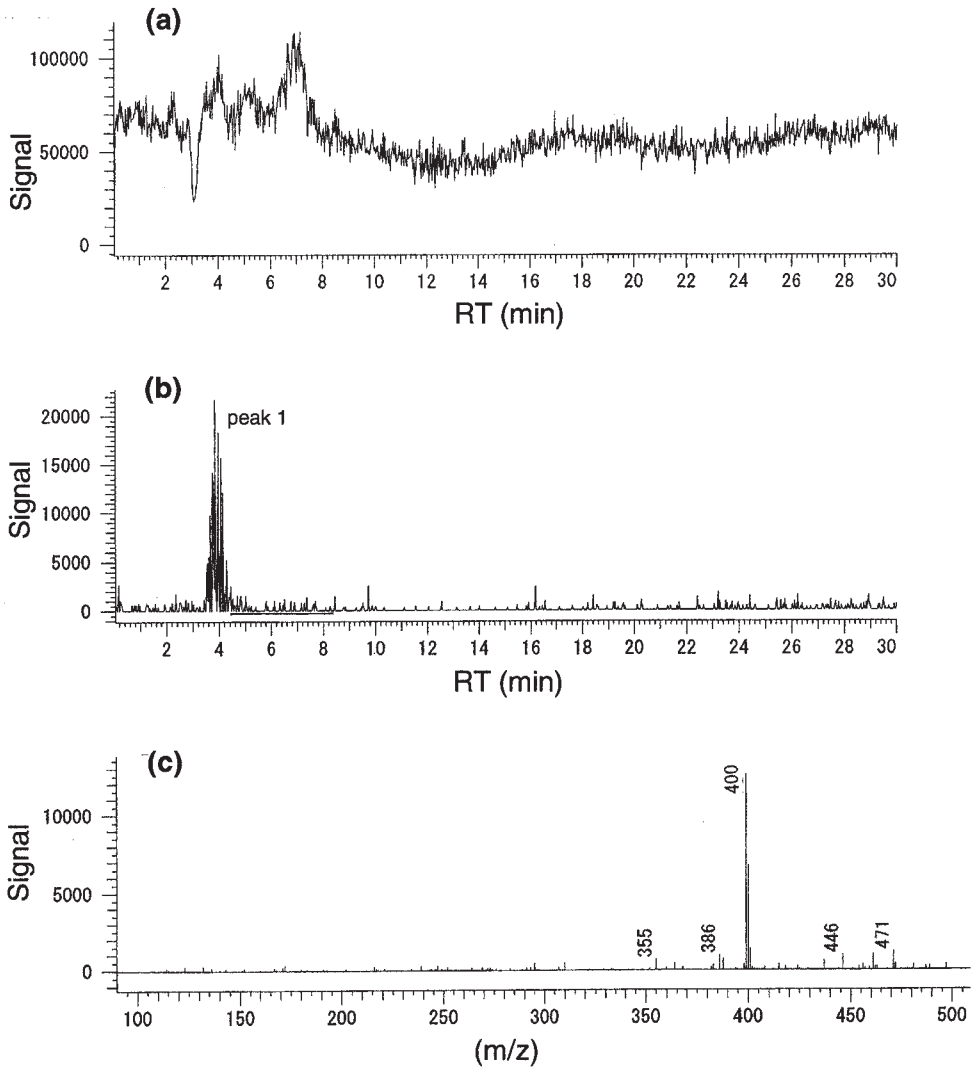

FIG. 4—*TIC of extract from the bile (a), HPLC—mass chromatogram of extract from the bile (b), and mass spectra of peak 1 (c).*

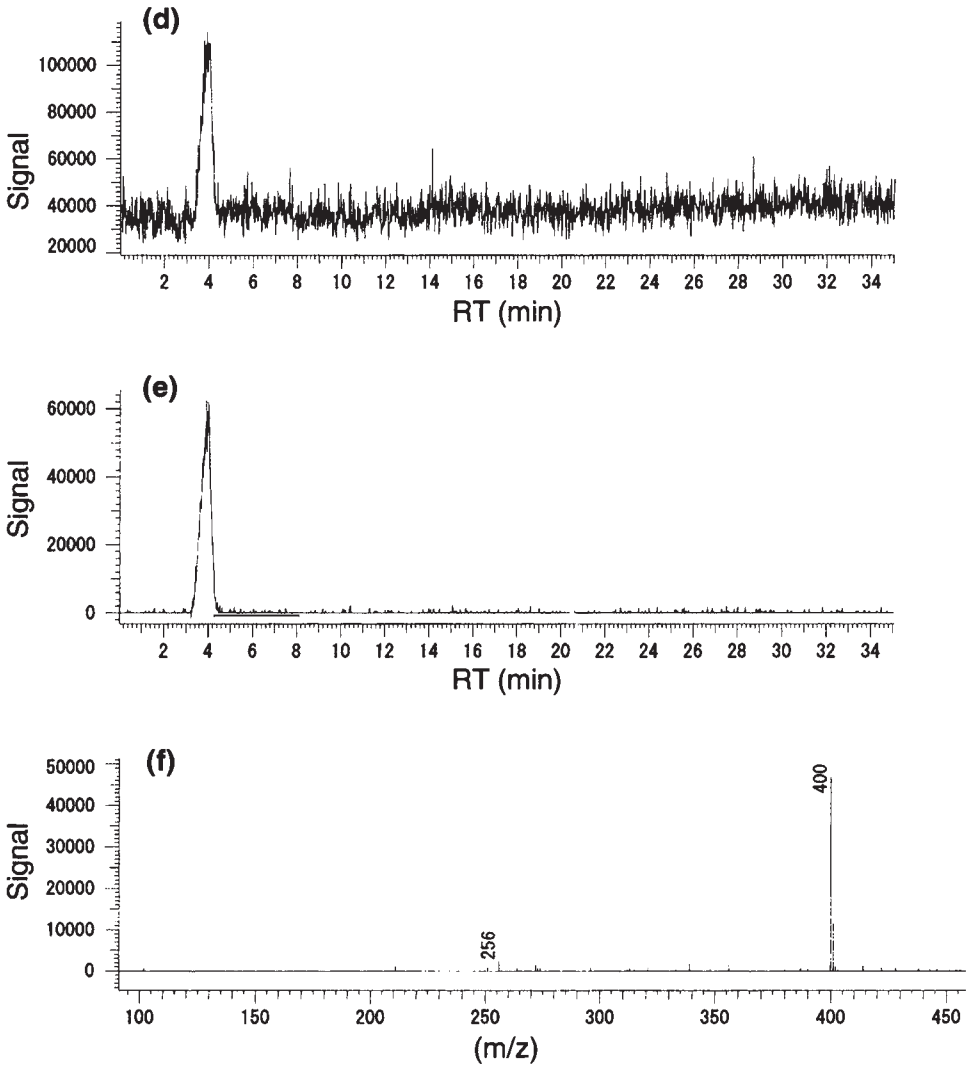

FIG. 4—*(continued) TIC of colchicine standard. (d), HPLC—mass chromatogram of colchicine standard (e), and mass spectra of the peak in Fig. 4*e *(f).*

TABLE 1—*Common complications of colchicine toxicity.*

Stage	Complication
1 (0–24 h)	Gastrointestinal symptoms, hypovolema, electrolyte balance disorders, peripheral leukocytosis
2 (Days 2,3,4,5,6,7)	Cardiovascular failure, adult respiratory distress syndrome, depressed level of consciousness, renal failure, consumptive coagulopathy, bone marrow depression, ileus, metabolic acidosis
3 (From the 7th day on)	Rebound leukocytosis, alopecia

References

1. Roll P, Klintschar M. Two cases of colchicine poisoning resulting from accidental ingestion of Meadow Saffron (*Colchicum Autumnale*). Proceedings of the International Association of Forensic Sciences 15th Triennial Meeting; 22–28 August 1999; Los Angeles. Los Angeles: The International Association of Forensic Sciences, 1999.
2. Allender WJ. Colchicine poisoning as a mode of suicide. J Forensic Sci 1982;27:944–7.
3. Folpini A, Furfori P. Colchicine toxicity: clinical features and treatment: Massive overdose case report. Clin Toxicol 1995;33:71–7.
4. Klintschar M, Beham-Schmidt C, Radner H, Henning G, Roll P. Colchicine poisoning by accidental ingestion of meadow saffron *(Colchicum autumnale):* pathological and medicolegal aspects. Forensic Sci Int 1999;106:191–200.
5. McIntyre IM, Ruszkiewicz AR, Crump K, Drummer OH. Death following colchicine poisoning. J Forensic Sci 1994;39:280–6.
6. Wells SR, Anderson DL. Colchicine toxicity: A case report. Vet Hum Toxicol 1989;31:313–6.
7. Yamada M, Nakagawa M, Haritani M, Kobayashi M, Furuoka H, Matsui T. Histopathological study of experimental acute poisoning of cattle by autumn crocus (*Colchicum autumnale L.*). J Vet Med Sci 1998;60: 949–52.
8. Clevenger CV, August TF, Shaw LM. Colchicine poisoning: report of a fatal case with body fluid analysis by GC/MS and histopathologic examination of postmortem tissues. J Anal Toxicol 1991;15:151–4.
9. Naidus RM, Rodvien R, Mielke CH Jr. Colchicine toxicity: A multisystem disease. Arch Intern Med 1977;137:394–6.
10. Wyngaarden JB. Gout. In: Wyngaarden JB, Smith LH, editors. Cecil's Textbook of Medicine, 16th edition, Vol. 1. Philadelphia London Toronto Mexico City Rio de Janeiro Sydney Tokyo: Saunders, 1982; 1107–17.
11. Rouan SKE, Otterness IG, Cunningham AC, Holden HE, Rhodes CT. Reversal of colchicine-induced mitotic arrest in chinese hamster cells with a colchicine specific monoclonal antibody. Am J Pathol 1990;137: 779–87.
12. Ellenhorn MJ, Schonwald S, Ordog G, Wasserberger J, editors. Ellenhorn's medical toxicology: diagnosis and treatment of human poisoning, 2nd edition. Baltimore Philadelphia London Paris Bangkok Buenos Aires Hong Kong Munich Sydney Tokyo Wroclaw: Williams & Wilkins, 1997.
13. Hobson CH, Rankin APN. A fatal colchicine overdose. Anaesth Intens Care 1986;14:453–64.
14. Borron SW, Scherrmann JM, Baud FJ. Markedly altered colchicine kinetics in a fatal intoxication: examination of contributing factors. Hum Exp Toxicol 1996;15:885–90.

Additional information and reprint requests:
Seiya Sannohe, M.D.
Department of Forensic Medicine
Hirosaki University School of Medicine
Zaifu-cho 5, Hirosaki, Aomori 036-8562
Japan