TORULOSIS OF THE CENTRAL NERVOUS SYSTEM*

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The two cases of torula involvement of the nervous system herein recorded presented a practically identical clinical, but a dissimilar gross pathological picture. This was in one case that of a cerebellar tumor and in the other that of disseminated involvement of the cerebrospinal system, including the cranial nerves, spinal roots and meninges. In both cases, repeated routine examinations of the spinal fluid gave essentially normal findings, and the course was chronic in Case 1 and acute in Case 2. In both cases a diagnosis of brain tumor was made and operations performed.

CASE REPORTS

Case 1. History. A white man, aged 49, had suffered from headaches since August 1943 (after a fall in which he struck his head). The headaches were often associated with nausea and vomiting which occasionally was projectile. There were exacerbations during which the patient was irrational, confused and agitated.

Examination. At the time of the patient's first hospitalization, Dec. 1943, neurologic examination revealed normal cranial nerves, including the condition of the pupils and the eye grounds; slightly decreased tendon reflexes in the upper extremities; brisk knee jerks; normal plantar's, and absence of cremasteric and abdominal reflexes. There was a "marked ataxia on standing," but no nystagmus or "signs of cerebellar disease." When in recumbent position, the patient's head and eyes were turned to the left, and bilateral Kernig and Brudzinski signs could be elicited.

Laboratory data: Blood—4,500,000 red cells and 22,000 white. Spinal fluid—Pressure, 24; 16 cells per cubic millimeter; Lange 001110000; the total protein, 50 mgm.; globulin, plus-minus; Wassermann test, negative.

Course. The patient's condition grew steadily worse. The weakness progressed; there was loss of 50 pounds in weight and six months following hospitalization he became unable to walk. He had been "comprehensively" examined in numerous hospitals but no definite diagnosis was arrived at. Four burr holes were made in the skull and normal findings revealed. The patient died two years after the onset of the headaches.

Necropsy. The gross findings were reported to me as follows: "The meninges, convolutions, sulci and ventricles were grossly normal. There were no atrophies or abnormalities in the hemispheres or brainstem, but the left cerebellar hemisphere was occupied by a well encapsulated tumor, the size of a hen's egg. The tumor was yellowish in color and firm to the touch but without evidences of hemorrhages, necrosis or cystic formations. The tumor deformed the lobe and displaced the pons and medulla to the right." Additional findings were—hypertrophy of the left myocardium; bronchopneumonia; adenoma of the adrenals and renal arteriosclerosis.

An ample supply of tissues from the brain and cerebellum was delivered to my laboratory in a 10 per cent solution of formalin. The cerebellar "tumor" was of cartilaginous consistency and at some points was rather loosely attached to the preserved parts of the cerebellum, and, as has been stated, showed no evidences of cysts, hemorrhages, softening or necrosis.

Microscopic observations: Examination of celloidin sections of the "tumor" stained with

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toluidin blue, thionin or methyl blue-eosin revealed dense foci (fig. 1) of large stellate formations (the upper part of the photomicrograph) traversed by bands of connective tissue (dark areas) and blood vessels. The stellate bodies appeared as though in pure cultures and each was enclosed in a round vacuole surrounded by a halo traversed by spines or spikes. Some vacuoles harbored as many as three bodies (fig. 2, at B) whose processes or spikes emanated from densely stained capsules occasionally forming anastomoses (at F). Some such formations exhibited distinct buddings (fig. 2, I, fig. 3, B) which were enclosed together with the cell bodies in one vacuole (fig. 3, B). Under higher magnification it was possible to observe in many instances homogeneous oval or round bodies (fig. 2, A.A.A., fig. 3, a.a.a., fig. 5, I) pinkish in color, only partly covered by a capsule (fig. 3, A\(^1\)) or wholly uncovered, that is, naked without any capsule whatever, freely scattered among the aforementioned

Fig. 1. Case 1. The upper portion of the photomicrograph shows masses of Torulae, a pure culture of them as it were. Underneath is the cerebellar substance exhibiting immensely infiltrated blood vessels. Toluidin blue stain.
stellate bodies. Such naked formations contained a double wall or membrane (figs. 4 and 5, at I) and were for the most part oval or round in shape and of small size. Only occasionally did such naked bodies exhibit spikes or spicules emanating from their walls (fig. 3, A'). Sometimes they appeared vacuolated or granular as if broken up. On the whole, the naked cell showed as typical Torula histolytica (Stoddard and Cotlar (1)) as generally pictured in specimens stained with hematoxylin-eosin (fig. 4), by the methods of Van Gieson or

![Figure 2](image-url)  
*Fig. 2. Torulae of Figure 1 under higher magnification. These appear as stars, covered with spikes, spines or spikules, some of which (F) are fused. At A.A.A., naked Torulae (without spines); B—three Torulae in one vacuole, and B' a larger one containing Torulae at the edges of the vacuole; I—a budding Torula. To be compared with Figure 4. Toluidin blue stain.*

Kernohan’s combined Bodian-Best stain, which methods fail to bring out the capsule or its spikes. As figure 4 shows, the naked Torulae are scattered in large numbers in the meshes formed by connective tissue fibers derived from the capsule of the tumor or its blood vessels. The Torulae were usually extracellular, but often intracellular, enclosed within giant cells. In some instances, the visual fields, even in toluidin blue-stained specimens, exhibited instead of Torulae broken up and granular spikes (fig. 5). These can well be seen in the right lower corner (at II), where the spikes of a Torula appear not in the form
of solid process but as granules which entirely resembled those scattered over the rest of the field mixed with naked Torulae and microglialocytes.

The cores of the cerebellar leaflets, that is the white substance bordering the tumor mass, showed numerous compound granular corpuscles (fig. 6 G) mostly of large size and inter-

![Diagram](image)

**Fig. 3. Case 1.** A—a vacuole harboring a stellate Torula, the rays or spikes of which almost reach the periphery of the vacuole; A’ A’—Torulae only partly covered with spines; B—a budding Torula within a vacuole; a a a—naked Torulae scattered among the vaculated ones; D—a foreign body giant cell enclosing two stellate and, in the crescent, many naked Torulae, (D). Toluidin blue stain.

mingled with cytoplasmic astrocytes, naked Torulae and more or less infiltrated blood vessels. In remote areas, the infiltrations were immense (fig. 7); the Virchow-Robin spaces were overflown by them, that is became extraadventitial and always contained Torulae.

The changes outlined were alike in the gray and white substances. The nerve cells within the Torula foci of the gray substance, often stained badly or did not stain at all and occasionally appeared as shadows, while other nerve cells appeared either normal or slightly tumefied.
Meninges—Figure 8 shows enormous infiltrations with lymphocytes and plasma cells resembling broad, dense gummatous masses. Beneath them can be seen foci of stellate Torulæ (T), and to the right there is a somewhat lighter area covered with small foci and many infiltrated blood vessels. No giant cells were detected in the enormously distended and infiltrated subarachnoid space but large numbers of them were present in the stroma of the choroid plexus. This contained numerous corpora arenacea and minute fragments of Torulæ within the tuft cells, many of which appeared as if plastered by them. The

tuft cells were sometimes lodged in the ventricular cavity in the form of small cast off heaps harboring Torulæ fragments. As the changes in the choroid plexus were more spectacular in Case 2, they will be discussed there in somewhat greater detail.

Case 2. History. A man, aged 46, was admitted to the Research Hospital, on March 6, 1945 in a semi-stuporous condition.

History. According to his relatives, the patient had never been sick, except for a “carbuncle” on the right cheek eight years previously. Three months prior to admission, he had a “boil” (on the left temple) which “disappeared after it was squeezed.” One month later, he complained of pain in the left side of the face which was followed by headaches, first frontal and later diffuse, and which extended to the “back, the neck and back of the head.”
Fig. 5. The field is densely covered with fragments of spines as describe, in the text. At I—a naked Torula, double contoured; II—broken-up spines, transformed into dots and granules resembling those in the rest of the field; III and IV—huge stellate Torulae within large vacuoles; all are provided with densely stained capsules and spines. Toluidin blue stain.

Fig. 6. From the neighborhood of the “tumor” mass (fig. 1). G—gitter cells, some harboring Torulae; the oval or round formation scattered throughout the visual field in the meshes are naked Torulae. Alzheimer-Mann stain.
Fig. 7. Adventitial and extraadventitial infiltrations of a number of blood vessels. In one to the right, several Torulæ may be seen in the infiltrations, mixed with plasma cells and lymphocytes. In the center of the picture there is a large light area showing microglial cells and plasma cells but no Torulæ. Toluidin-blue stain.

A week before admission to the hospital the patient became disoriented and his vision and hearing impaired.

Examination. The patient was drowsy and therefore cooperated poorly. He exhibited
a Kernig and Brudzinski signs, a bilateral papilledema of three diopters with a "noticeable retinal hemorrhage." The right pupil was larger than the left and all the cranial nerves appeared to be normal. The tendon reflexes were present in the upper and absent in the lower extremities; the abdominal reflexes were weak on the right, where Babinski, Chad-dock and similar signs could be elicited. The bladder and rectal functions were normal.

Fig. 8. Case 1. Changes in the meninges. The dense masses in the upper left corner are infiltrated blood vessels (lymphocytes and plasma cells) described in the text. The rest of the picture shows foci of Torula (T.T.) mixed with blood vessels, for the most part infiltrated. Toluidin blue stain.

The blood pressure was 124 systolic and 90 diastolic; the heart, lungs and viscera showed no abnormalities.

Laboratory data: Blood—Hemoglobin, 16.5; red cells, 5,330,000; leucocytes, 6700; the Wassermann and Kahn tests, negative. Urine, normal. The spinal fluid (ventricular)—Total protein 0.4 and 0.013, Pandy 2+ and no cells.

The patient grew irritable, restless, noisy and had to be restrained. Burr holes were placed in the skull and revealed a tense dura mater. Death occurred on March 20, 1945.

Pathologic observations. No gross changes in the brain or spinal cord were in evidence.

Microscopic observations. Throughout the brain, as described in the previous case, dense foci of stellate Torulae were scattered. The foci appeared (in toluidin blue sections) not
as cysts but as dense masses (fig. 9, top), some large, others minute consisting only of a few Torulae. Single torulae were seen scattered throughout the visual field, and are well seen as black dots in the right upper corner of the photomierograph. In sections stained by the

method of Van Gieson or hematoxylin-eosin, the foci presented entirely different aspects. They appeared honeycombed (fig. 9, bottom), made up of minute vacuoles, each harboring a Torula, the picture probably resembling what Freeman (3) described as "soap-suds" or "soap bubbles". The surrounding parenchyma exhibited no changes which, however, could be demonstrated in the adjacent areas. A common occurrence was microgliocytes,
intermingled with cytoplasmic astrocytes and plasma cells. These were detached from the blood vessels or capillaries and often were arranged as strings in the parenchyma. The

ganglion cells were for the most part preserved, but within the foci themselves they were always more or less changed; they appeared pale, tumeied or as cell shadows. The nuclei were shrunken, devoid of chromatin or in a state of caryolysis. Blood vessels which were

Fig. 10. Top: Meninges of the base of the cerebellum—immense infiltrations of the subarachnoid space with Torulae. F.F.F.—small foci of Torulae in the cerebellum without reactive phenomena; N—focus of necrosis. Toluidin blue stain.
Bottom: Meningitis. Foreign body giant cells in pure culture containing Torulae. Toluidin blue stain.
quite promiscuous in some foci, were massively infiltrated with plasma cells and lymphocytes, the infiltration cells in some instances forming as many as sixteen parallel rows. Newly formed blood vessels were in evidence, mostly as buddings or were arranged as string-

![Fig. 11. The choroid plexus. The tuft cells contain particles of Torulae. B—Torulae within the lumen of a blood vessel; V—ventricular cavity containing fairly well preserved Torulae, at V¹ mixed with cast off tuft cells. E—ependyma with dust-like granules in some of its cells; E¹—subependymal tissue.](image)

like fibroblasts. In contrast with such areas rich in Torulae, blood vessels and reactive changes, other areas appeared necrotic, as dust-like material, scattered among Torulae, for the most part broken up, disfigured, shrunken and devoid of membranes. Such frag-
mented parasites were occasionally mixed in some smaller foci with ganglion cells, com-
ound granular corpuscles and plasma cells.

Meninges. The cerebral subarachnoid spaces were distended by large bulging masses of Torulae (fig. 10, top) and exhibited rarefied areas of necrosis (N). The masses were sharply delimited from the cerebellum where minute foci (F) were present harboring Torulae. The main, if not the exclusive, cell bodies of the space were foreign body giant cells (fig. 10, the bottom photomicrograph), all packed with stellate and naked Torulae. Here one may see as many as seventeen parasites in one giant cell, two of them exhibiting spikes and capsules, one giant cell containing six stellate parasites and the majority, both forms. Some Torulae lay free among the giant cells.

Instructive changes were present in the choroid plexuses. The tuft cells (fig. 11) har-
bored minute particles of Torulae in the form of black dots which also were present in the

Fig. 12. The oculomotor nerve. Foci of Torulae among the nerve bundles and even among single nerve fibers. At the extreme right a soap bubble appearance is suggestive. Toluadin blue stain.

lumina of the blood vessels (B) and as larger fragments but not as fully developed organisms in the cavities of the ventricles themselves (V). In the ependymal covering (E) only dust-
like granules were present and a few somewhat coarser ones in the subependymal tissues (E'). Also striking was invasion of the cranial nerves by Torulae. Large accumulations of them can be seen in figure 12, gathered among the bundles of the fibers of the oculomotor nerve and even among single nerve fibers where they can be traced as dots. The bundle to the left shows compact nerve fibers, while to the extreme right the changes appear as soap-suds.

Spinal cord. The spinal subarachnoid space, like the cerebral one, was filled with Torul-
lae which densely covered the trabeculae and, as in the cerebral subarachnoid space, ob-
scured the structures. On the whole, the infiltrations of the spinal meninges were less dense than those of the brain. In the parenchyma of the spinal cord the Torulae appeared as strings of single parasites over the margins of the spinal cord without reactive changes on the part of the blood vessels or glia. Microgliocytes, however, were conspicuous through-
out the parenchyma. Torulae were gathered in large numbers in the spinal roots, especially in the perineurium where they were mixed with lymphocytes, plasma cells, and basophil metachromatic substances. It was not possible to ascertain the exact location of these substances—whether in the Schwann cells, perineurium or around the blood vessels. The Torulae in the spinal roots and meninges were both naked and stellate, were usually lodged in vacuoles, and not in giant cells which were absent in the areas mentioned.

COMMENT

Of the two cases under discussion one was acute, approximately of two months' duration; the other was chronic and probably lasted three years. In Piper's (4) patient, the known period was eleven days, but the "patient may have been sick before he consulted his doctor." Thus, torulosis, which is essentially a chronic disease process, may run an acute course and yet give a clinical picture of the chronic type. It is to be noted that the eye fundi, which were normal in the first case—that of a vast cerebellar tumor of long standing—exhibited papilledema in the second, acute case where the changes were as scattered foci of nerve destruction. However, in both cases a diagnosis of increased intracranial pressure was justified and surgical intervention indicated. The tumor in Case 1 was at some points loosely connected with the cerebellar tissue, as was the case also in the patient of Swanson and Smith (5). The tumor, they stated, showed "a striking tendency to separate easily from the surrounding tissue with little or no evidence of active invasion or reaction other than pressure necrosis." One could hardly hope for a successful removal of the tumor, at least in my case, as small foci of Torulae were present in the grossly preserved portions of the cerebellum, pons and elsewhere in the brain stem. It should be emphasized that a localized torulosis, in the form of a tumor, is rare. Only three cases have been recorded—by Dickinson, Veppe and Negri (6) (a cerebellar tumor), Swanson and Smith (5) (one tumor was in the cerebellum and two in the occipital lobe) and one by Smith and Crawford (7) (the tumor was in the spinal cord). One should bear in mind the possibility of a torular involvement of the nervous system even in cases of an apparently acute onset and one should, therefore, examine the spinal fluid for the possible presence of Torulae. In my two cases the results of an ordinary examination of spinal fluid were of little, if any, help. For instance, there was in one case only a slight increase in cells in the spinal fluid and no cells were found in the second case. This may be explained by the fact that lymphocytes and plasma cells were scarce in the subarachnoid space where the predominant elements were Torulae, for the most part lodged in foreign body giant cells. Many sections showed nothing but giant cells which elements, probably due to their size do not land in the spinal fluid obtained by a spinal puncture.

The ubiquitous presence of immense masses of Torulae in the nervous system overshadows other pathologic phenomena, reactive, for instance. In the tumor mass itself, bands of connective tissue derived from its capsule or the blood vessel walls were found to be infiltrated with lymphocytes and plasma cells. The infiltrations were sometimes enormous, never contained histiocytes, compound granular corpuscles, giant cells or cheesy material. In short, they were not analogous to the granulomatous masses seen in syphilitic, tuberculous or other
chronic toxic-infectious states. For this reason, it would be improper to speak of a torulous granuloma, but of an intense plain inflammatory reaction.

The presence of fragments of Torulae in the cytoplasm of the tuft cells of the choroid plexuses (fig. 11) should be considered of significance. In both of my cases the fragments, as has been stated, were within the tuft cells, occasionally in the lumina of the blood vessels of the tufts, while the ventricular cavities themselves contained, in addition, fairly well preserved Torulae, some in contact with the tufts. It is only logical to assume that the torula fragments landed in the tuft cells from the ventricular cavity. As has repeatedly been stated elsewhere (8), the tuft cells of the choroid plexus do not secrete cerebrospinal fluid which, in my opinion, represents the tissue fluids of the cerebral or spinal cord parenchyma discharged into the subarachnoid space and ventricles, loaded with catabolic products. These are excreted or extracted by the tuft cells and rendered harmless, the spinal fluid being made more absorbable. The presence of dust-like granules in the ependymal cells also may be considered derivatives of Torulae which invaded them from the subependymal parenchyma.

The morphology of the Torulae in the cases under discussion deserves a special discussion. Torulae are generally pictured as oval, round double-walled or contoured bodies of small or large size, depressed in the center which is paler than the rim. The Torulae are lodged within small cystic cavities described by de Crespigni (9) as "a tunnelling of white ants (on a minute scale)." The contents of the cysts were classified as gelatinous, jelly-like, mucous, colloid (Semera (10)) or starchy (Blair (11)). There was no gross evidence of gelatin or any other substance or gross cavities in the present cases, probably because the brains were seen by me after they had been in formalin for some time, though, according to Freeman (3), not in all brains has the presence of cavities been recorded. Weil (12) is of the opinion that in alcohol-fixed material they are not found, but are present only in formalin-fixed tissues, as the formalin dissolves the gelatinous material. Neither cavities, capsules nor spikes have been described in other equally common types of fungi, such as Cocciidioides immitis or Blastomyctes (Oidium). In the case of Cocciidioides which I studied the foregoing formations were not seen. Rixford (13), however, occasionally saw "prickles" in his cases, but only in about three instances among "many hundreds of protozoa studies." Ophules (14) called them bristles, which were also seen (in Cocciidioidosis) by Ahlfeld (15), Wohlbach (16), Evans (17), Dixon (18) and were described by some as radiating prickles. In Oidium or Blastomyctosis spicules or spines have not been described at all, mycelia being considered typical of this type of fungus which does not affect the nervous system but only the skin. LeCount (19), however, described a cerebellar involvement in Blastomyctosis and in Rappaport and Kaplan's case (20) of Torulosis, which affects the nervous system, the skin also was involved. Exceptions thus occur as to the localization and distribution of changes, but there is no exception as to the morphology of the Torula. Its capsule and spikes are typical, provided toluidin blue, thionin or methylblue or similar anilin dyes are used. The bristles pictured by Rixford (his fig. 17 in plate 29) even do not resemble the spikes of Torula. Watts (21) well described them as
“radially arranged with a broad base attached to the outer wall of the organism and a pointed end.” In contrast, the bristles of Coccidioides immitis are thin uniform and very sparse. As far back as 1907, Benda (22), in a case he classified as "Blastomycosis", describes the spines as "picturesque rays emanating from cytoplasm" surrounding the capsule on all sides and... become continuous with similar rays of the neighborhood cells"—a fact he adds not yet observed in fungi. The stains used by Benda were toluidin blue or methylene-blue-eosin. Freeman (3) asserts that toluidin blue shows them "occasionally," Stoddard and Cutler devote to them a few lines and Shapiro and O'Neal (23) state that they obtained much better results from methylene-blue-eosin than from hematoxylin-eosin, which also did not satisfy Langmire and Goodwin (24). It is interesting that in their recent monograph Cox and Tolhurst (25) mention "Striations" or "furiness" which "they believe due to distortion." This may be explained by the fact that they used only hematoxylin-eosin for tissue staining. A splendid discription and interpretation of Torulae are given by de Busscher, Scherer and Thomas (25-a) whose findings are largely confirmed by mine. Their article came to my notice after my manuscript had been sent to the printers. In some Torulæ, as our figure 5 shows, the spikes appear granular. Granules, as has been stated, covered the larger portions of the visual field evidently being a manifestation of regressive changes taking place in the Torulæ. This probably would speak against an assumption that the spikes and the capsule itself are gelatinous, as in my experience gelatin does not appear granular, at least with the methods of embedding and staining generally used. Nor does gelatin stain as densely with toluidin blue as does Torula histolytica, nor does it shrink. It also would be difficult to explain the presence of the gelatinous spikes and capsules in the subarachnoid space and giant cells where cysts filled with gelatin do not exist. For the foregoing reasons, one cannot consider the spikes and the capsules the consequence of shrinkage of the "gelatine" or "colloid" masses. In short, the real nature of the contents of the cysts, vacuoles, capsules or the spikes is not known.

The explanation given by Rixford (and later by Stoddard and Cutler (1)) that the substance "may be due to secretion produced by the parasite in order to protect itself from the attacks of the surrounding epithelial cells" is probably correct but one would wonder at the lack of such a protection in other types of fungi. It is noteworthy that small sized Torulæ, as a rule, possess no capsule or spikes.

The last noteworthy pathologic feature is the type and cause of nerve destruction, whether it is due to pressure by the Torulæ (McKendree and Cornwall (26), Blair (11)) or some chemical process causing lysis (Sheppe (27)). Pressure may be considered a cause if the foci are large, but when these are minute (fig. 10) such a factor can hardly be at play, for a few torulæ cannot cause nerve destruction. In the neighborhood of the tumor mass (fig. 6) compound granular corpuscles, as has been stated, were combined with cytoplasmic astrocytes and intense perivascular lymphocytic and plasma cell infiltrations which, in areas remote from the tumor, also were scattered throughout the parenchyma. Such
changes would be more compatible with those caused by an infection or intoxication—common causes of destruction of nerve parenchyma. As the actual cause is not established, there is a tendency to deny the Torula the ability to dissolve nerve tissue, to consider the term Torula histolytica a misnomer and to substitute other names, such as Cryptococcus hominis or Debaryomyces neoformans. Some mycologists, however, (Benham (28)) consider the strains of cryptococcus hominis (the yeast of European blastomycosis) and those of Torula histolytica essentially identical formations, the difference in the pathogenicity being one of degree only.

CONCLUSIONS

1. Torulosis of the central nervous system in humans may run an acute course and give a clinical picture of increased intracranial pressure (cerebral tumor or abcess).

2. Pathologically, Torulosis may manifest itself as a localized lesion (tumor), but in association with remote foci throughout the central nervous system, including the ventricles, choroid plexuses, meninges, spinal roots and cranial nerves.

3. Anilin dyes (toluidin blue, thionin, methyl blue) bring out in a Torula the presence of a capsule supplied with numerous spikes, spines or spicules and also of Torulae deprived of capsules as usually seen when hematoxylin-eosin stain is used (so-called naked Torulae).

4. A single Torula or small torular foci produce no reactive changes which, however, are present around large foci or in their vicinity in the form of large infiltrations.

5. Fragments of Torulae are present within the tuft cells of the choroid plexuses—an additional proof that the function of the choroid plexus is excretory and not secretory.

REFERENCES


